"The Mode of Action of Local Anaesthetics".

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Philip J. Watson B.Sc.(Hons.) Physiology
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INTRODUCTION.

It has been known for a considerable time that certain drugs produce a localized loss of sensation, but attention was first focussed on this subject in 1860 by Niemann, when he isolated the alkaloid cocaine from the leaves of Erythroxylon coca. He reported that cocaine "benumbs the nerves of the tongue, depriving it of feeling and taste". In 1884 Koller introduced cocaine as a local anaesthetic in ophthalmic work, and its use spread later to general surgery.

Various attempts have been made to explain the mode of action of such drugs, but no clear cut case has yet been made out. This may be partly due to the fact that local anaesthetics have not commanded the attention that has been accorded to the general anaesthetics. This is scarcely surprising, because the birth of surgical anaesthesia in the 1840s was such a revolutionary event: as the general anaesthetic produces complete relief from pain for the whole body, it was bound to attract more attention than the local anaesthetic which only affects a limited area.

Bernard, in 1875 (16) insisted that all agents which depress nerve cells, including heat and asphyxia, do so by producing the same modification in the cell, and, moreover, depress every manifestation of life whatever, i.e. there is a single and universal mechanism of narcosis. 75 years later, Butler (37) expressed dissatisfaction with a concept of one all-inclusive phenomenon of narcosis: he took the view that when two different drugs produce the same

apparent effect, it is not justifiable to assume, without further evidence, that the same mechanism is involved in both cases.

Between the observations of Bernard and Butler many investigations have been carried out upon general anaesth--etics, and various theories have been advanced about their modes of action. Amongst the more notable were those of Meyer and Overton, Traube, Warburg, and more recently, that of Ferguson.

It is inevitable that, as both general and local anaesth--esia relate to the action of drugs on nervous tissue, theories about the former should be carried into the realms of local anaesthesia, and must merit serious consideration in any study of mode of action. At the same time it is obvious that attention must also be paid to the means of transmission of nerve impulses, as there may well be factors involved in this process which aid, or blend with, the action of the drug in producing a local anaesthetic effect. Thus, data for the present study can be divided into three main sections:-

1. Information derived from, or common with, general anaesthesia.
2. Information from work on local anaesthetics themselves.
3. Information about the nerve impulse which may relate to local anaesthesia.

In the present treatise it is proposed to deal with the subject matter as follows:-

a. Transmission of the nerve impulse.

b. Relevance of the theories of general anaesthesia to local anaesthesia.

c. Other factors which seem to be important in local anaesthesia.

d. Discussion of various questions raised.

TRANSMISSION OF THE NERVE IMPULSE.

It is not in the province of this review to discuss the various theories of transmission at length. Nevertheless, a brief description of current ideas is necessary for reference in the later sections, together with a note of some views having a bearing upon researches in local anaes--thesia.

It has long been known that there is a potential differ-ence across the membrane of the resting nerve, the proto--plasm being negative and the interstitial tissue fluid positive. The first serious attempt to explain this was by Bernstein (17,18), who observed that the concentration of potassium ions is considerably greater inside nerve fibres than outside: he considered that, if the membrane is impermeable to anions and to sodium ions, the difference between the concentrations of potassium internally and externally would explain the resting potential. He believed that, during activity, the selective permeability for potassium collapses, and the membrane potential consequently approaches zero.

Later the theory was modified, but, despite this, Lorente de Nó in 1947 (167) still considered that it fails to

explain the resting membrane potential, although Höber et al. in 1939 (114) had firmly expressed the view that excitation consists of a chemical and physico-chemical wave spreading along the nerve, and that it is correlated with a breakdown of the structure of the fibre surface.

Lorente de Nó rejected the hypothesis on the grounds of the relative unimportance of potassium, derived from the observation that nerves kept anoxic in potassium-free media for 12-15 hours showed complete repolarization within a few minutes of restoring oxygen to the nerve. Similar effects were seen when sodium-deficient nerves were exposed to the air (171), but Krnjevic (147) believed that this was largely caused by a drying effect, and the same might be true of the potassium experiment.

Although he rejected the theory, Lorente de Nó admitted that the mechanism underlying nerve impulse production is inoper--ative unless sodium is available to the nerve, since it affects excitability, and unless the membrane potential is at, or above, a certain critical level. He conceded, moreover, that nerve cannot be fully independent of potassium, since excess of it produces depolarization, and also that internal potassium effects may have some importance, although he claimed that the latter is subordinate to the effect of oxidative metabolism.

The importance of Bernstein's concept lies in the suggestion that ionic concentrations govern the creation and/ or the maintenance of definite electrical conditions.

Hodgkin, Huxley, Katz, and others, adopted this premise in formulating the present commonly-accepted theory of nerve conduction. First doubts about the full validity of Bernstein's hypothesis arose from the observations by Hodgkin and Huxley (118,119) and Curtis and Cole (43,44) that the membrane potential of squid giant axon does not merely drop to zero at the peak of the action spike, but is substantially reversed, and this was subsequently shown to be true of almost every type of excitable cell, vertebrate or inverte-
-brate.

In 1947 Hodgkin and Huxley (120) presented considerable evidence for the liberation of potassium during the passage of the nerve impulse. As regards the resting potential, they considered that the nerve exhibits a continous energy expenditure, this metabolic action being directed towards the uptake of potassium: opposing this is a high intrace-
-llular potassium concentration which tends to escape from the nerve fibre at a rate determined by the concentration (or activity) gradient, and by the permeability. Under resting conditions the balance between metabolic and physical forces would contribute to the steep potassium gradient in the membrane, and hence to a low surface concentration. The potassium restoration mechanism at the surface may be activ-
-ated by the escape of potassium from inside, such as occurs during the passage of the nerve impulse. Quite naturally, since a metabolic activity was stipulated, it was considered that anoxia would stop the compensatory aerobic action.

In 1949 Hodgkin and Katz (121) suggested that the action potential of nerve is due to the shift of sodium ions. This appeared to support a theory which had been developed by Hodgkin and Huxley to account for the "discrepancies" in the change in resting membrane potential during activity: according to this, the rising phase of the spike results from a specific increase in the sodium permeability of the membrane, while the potassium permeability is increased above normal during the falling phase. Further evidence has accumulated to support their ideas, derived from measurements of the ionic movements during nervous activity, both by means of indirect methods, and by the use of radioactive tracers: details are given by Hodgkin in his review (116), and also by Hodgkin and Keynes (122).

Most of this work was carried out upon squid tissue, and Keynes (139) has warned that it would be dangerous to assume that an identical series of events occurs during impulse conduction along other types of nerve and muscle fibres.

Barlow, in 1955 (9), observed that, in a resting nerve, external sodium ions give a positive charge to the outside of the cell (Boyle and Conway (26) demonstrated the same effect in muscle), but after stimulation the ionic positions are reversed with sodium inside and potassium outside. Unlike Gray and Geddes (91) who envisaged recovery as a restoration of the potassium balance by a form of pumping action, he was convinced that a dual problem exists, not merely that of getting potassium in, but also of sodium extrusion.

If the modified Bernstein theory is true, the contention

by Barlow, that any agent which interferes with ionic concentrations, membrane permeability, or metabolic reactions (particularly those involved in the recovery process), must possess latent blocking powers, is obviously correct. Consid--erable confirmation has been obtained for this view (117). It seems that, despite Keynes' doubts, most nerves work in essentially the same manner as those of squid. The high internal potassium is balanced by organic anions supplied by substances such as aspartic and glutamic acids, while iseth--ionic acid was considered by Koechlin (145) to be particul--arly important in squid, and probably also in vertebrate, nerves. The potassium ions are free, and are not bound to proteins or other large molecules.

On stimulation, activity is triggered by the spread of electrical current from a neighbouring region. It is accom--panied by permeability changes in the membrane which breaks down partially or completely, the whole process being marked by definite electrical changes. The positive internal deflec--tion observed is probably due to sodium ion entry, as it is absent in sodium-free solutions, and the changes in current are subsequently continued by an outward movement of potass--ium ions. The sodium changes provide the current required to depolarize the resting membrane ahead of the active region. After the changes, the nerve fairly quickly returns to normal and can conduct another impulse, the fibre having gained a small quantity of sodium and having lost a similar one of potassium. The ionic movements are the immediate energy source for impulse conduction, and are reversed later by a

slow process requiring metabolic energy. Hodgkin (117) has claimed that a large fibre may take several hours to wipe out the effects of short bursts of electrical activity. He also stated that it seems likely that sodium and potassium move--ments are involved in many cells, although the action poten--tial of heart muscle is about three hundred times that of squid giant axon, whilst Katz (137) has reported that, in striated muscle the membrane rectifies direct current in the opposite direction to that found in nerve. The important inference of the last is unavoidable, and must be borne in mind in studying results relating muscle and nerve in later sections.

It is also clear from Hodgkin's review that sodium and potassium can be influenced by temperature, membrane potent--ial, and calcium concentration. The last is interesting. Keynes and Lewis (140) have shown that the total internal concentration of this ion may be about one thirtieth of that outside, and it has been recently suggested (123) that the figure for internal un-ionized calcium is about one thous--andth of that on the outside. If this is true it seems as if there is some mechanism which controls calcium values about the nerve. Low calcium values produce an increase in sodium conductance, i.e. excitability. Hodgkin (117) suggested that calcium is adsorbed on the membrane, thereby altering the local electric field inside the membrane with--out changing the overall potential difference between inside and outside. "In this case, calcium ions would be

important in so far as their concentration influenced the permeability and excitability of the membrane, but they could not be regarded as taking any very direct part in the conduction of impulses."

A small amount of calcium (c.1/700 th. of the total sodium entry) enters squid nerve when it conducts an impulse (68, 123), but resting fibre is only very sparingly permeable to this ion. Hodgkin conceded that calcium movements may have a connection with changes in permeability, because there are axoplasmic substances with a high calcium affinity. He conceived that depolarization allows calcium to be handed on from the membrane to the axoplasm, and that this reaction liberates carriers which transport sodium ions through the membrane: however, it fails to explain the low calcium effect. The reference to permeability is notable.

He also suggested that there are special channels allowing sodium and potassium to move at varying rates down their concentration gradients. Thus..... "When the nerve conducts an impulse, the channels open up, allowing first sodium ions, and then potassium ions, to move down their concentration gradients. These movements generate the action potential, and the fibre pays by accumulating sodium and losing potass--ium".

The account above embodies the main principles of modern theory, but it is necessary to mention other work which is linked, directly or indirectly, with some of the work to be described later.

The hollow core theory of conduction is associated with the name of Cremer: the nerve fibre is regarded as a cored conductor, the centre of the axis cylinder being surrounded by a more or less insulating layer of lipoid (the membrane), beyond which there is an external longitudinal conductor in the shape of the interstitial tissue fluid. Lorente de Nó (167) claimed that nerve membrane need not be identified with structural layers which are recognizable in anatomical prep--arations, because its properties are functional ones. How--ever, Robertson (223) has recently claimed that there is, in fact, a definite membrane around the axon.

With the advent of a theory based on properties of this sort it was natural that attempts should be made to produce models which would function in the same way. The most famous one was devised by Lillie (161): an iron wire was immersed briefly in strong nitric acid, causing a film of iron oxide to be formed at the surface. Unlike an untreated one, if the wire was then transferred to dilute nitric acid, no reac--tion occurred. This, then, represented the resting nerve, the wire being the core, the oxide film the membrane, and the dilute acid the surrounding fluid. It could be stimulated in a variety of ways, e. g. mechanically breaking the protective oxide film, or by applying an electric current to it. Upon stimulation a reaction (electrochemical reduction) was set up, accompanied by effervescence and the formation of a dark coloured lower oxide, which swept down the wire: if two parts of the wire were linked to a galvanometer a current flow could be detected during this spread of the reaction.

If the acid was of a certain concentration the protective film re-formed in the wake of the reaction. A second stimu-lus was ineffective until the film had been restored. As long as the protective oxide film was intact a potential difference existed between the wire on the inside and the surrounding acid: discontinuity at any point in the film made this region negative to the others and could block the excitation wave in its progress to the end of the wire. Finally, it was claimed that the rate of propagation was of the same order as that of the nerve impulse.

Hirschfelder and Bieter (111) believed that the alterations in the surface layer of this model are indeed analogous to the passage of the action current in a nerve fibre. They thought that in the latter an increase occurs in the perm-eability of the lipoid surface layer. From this they con-cluded that, in general, substances which increase the perm-eability of the lipoid layer (in concentrations less than those which destroy it) might be expected to increase nerve actions and sensations, while those which decrease the perm-eability to water and ions might be expected to act as anaes-thetics.

It is very striking that two theories, the one (by Bern-stein) starting as an attempt to explain the membrane rest-int potential, and the other (by Cremer) the mode of con-duction of the impulse, should stress the importance of the same factor, namely, permeability. However, to accept this conclusion of Hirschfelder and Bieter per se is to be very

previous, and further evidence is essential.

A fundamental question which the differential effects of local anaesthetics is bound to pose is whether peripheral nerves differ anatomically or physiologically. Obviously the possession of myelin creates a major distinction in the types of nerve, but if, as is generally thought, its function is of an acceleratory nature the difference may not be so great as might at first be expected.

Gasser and Erlanger (78) cited work showing that axon potentials and refractory phases are the same in all medullated fibres greater than 5 microns in diameter, and possibly in some smaller fibres also: they therefore suggested that the fundamental chemical or physico-chemical constitution of nerve fibres is the same in all above this size. They claimed that the variable effects are the threshold of excitation and the velocity of conduction, which both depend upon fibre size. Hence, the order in which fibres are blocked may be a linear function of their diameter: this may be translated into observations on the conducted action potential in terms of the time difference which distinguishes fast and slow fibres.

Bishop (23) concluded that resting potential and action potential are both related to the steady state of nerve, but he considered that the two are not necessarily reciprocal functions of the same reaction, nor need they vary in exact proportion. He did not believe that depression of either is an immediate cause of failure of the nerve response.

He reported that both asphyxia and carbon dioxide are more potent than crushing in converting a diphasic nerve response to a monophasic one, and he considered that all depressant agents work similarly. It is debatable if the production of monophasic responses can legitimately be compared with block-ing effects, but the importance of the observation lies in the implication of a metabolic effect.

This had already been mooted elsewhere: Koch in 1927 (142) noted a decrease in resting potential accompanying the loss of excitability in rabbit nerve deprived of its blood supply, and Gerard (80) reported a potential difference between an area of frog nerve in nitrogen and one in oxygen. Wright (300) deduced that the primary effect of anoxia upon nerve fibres consists of depolarization of their membranes: when it has been carried far enough impulse propagation becomes im-possible. He quoted the disappearance of the action pot-ential spike in carbon monoxide reported by Schmitt (229), in cyanide by Schmitt and Schmitt (231), and in alcohol by Davis et al.(45). The last leads into the realms of the narcotic drugs, hence the link with the present work is sig-nificant.

Wright sought to discover if the compounds cited above act by depolarization or by directly blocking conduction in fibres which remain polarized. All ultimately produced depolarization, but alcohol also tended to increase the exc-itability threshold, which Wright attributed to a direct action on the chemical structure of the nerve membrane.

From his results he named two classes of depolarizing drug:-

a) The asphyxiants, e. g. carbon monoxide, nitrogen, hydrogen cyanide, which prevent oxygen utilization. These show little threshold (excitability) change until a sudden rise at the point of conduction extinction.

b) The narcotics e. g. alcohol, which cause a slow but continous threshold increase.

He was unable to explain why a narcotized nerve only recovers slowly in oxygen, whereas an asphyxiated one in similar circumstances recovers abruptly.

Lorente de Nó (167), however, concluded that, by itself, lack of oxygen is insufficient to bring about a total depolarization of nerve. This certainly appears to reduce the importance of aerobic metabolic activity in this respect, but does not preclude a blocking effect without depolarization, Indeed, an earlier view, that transmission block may be due to a direct action on cell metabolism (66) has recently been endorsed (208).

Despite the theories of Weiss (290) against an axial current flow, Lorente de Nó claimed that the flow of longitudinal current results in the appearance of longitudinal electromotive forces in the core of nerve fibres. In his opinion, the existence of the connective tissue sheath can be ignored in surface potential analysis, despite claims by other authors that it distorts the potential difference thus obtained. This last assertion deserves comment, because it depends on the thesis that nerve connective tissue sheaths present little or no electrical or diffusion resistance.

He still held this view in the face of a growing body of evidence, dating from 1807 onwards, that the sheath is a diffusion barrier and has a high electrical resistance. Bishop et al.(24) in 1926 suggested that many "nerve" properties might be features of this non-nervous structure. In 1949 Feng and Liu (59) and Rashbass and Rushton (213) produced comparisions of intact and desheathed frog nerves. Results of the latter authors revealed a close conformity with the simple cable theory when the epineurium was removed. (Later histological work by Krnjevic (148) suggested that the perineurium, rather than the epineurium, is the barrier to diffusion, but, most significantly, he pointed out that desheathing always removes the perineurium. He further drew attention to the similarity between it and the arachnoid membrane of the brain, even to the point of suggesting that they have a common embryological history). Rashbass and Rushton claimed their results reflected doubts about many of Lorente de Nó's conclusions, especially as they believed that his "longitudinal polarization" is a feature of the epineurium and not the nerve. (In Chapter X of his monograph Lorente de Nó appears to admit that, in fact, the core is not polarizable.) They endorsed earlier views (24) that much work on nerve resistance, permeability, electrotonus, and polarization, needs re-interpretation in the light of the possible effects of a highly polarizable resistance being interposed between the nerve axon and the electrode.

Despite such objections, Lorente de Nó continued to reject such evidence, describing desheathed nerve as

"abnormal". Krnjevic (147) obviated this criticism by working with perfused nerves, which sucessfully brought drugs into intimate contact with nerve tissue, at the same time evading any effect produced by the sheath. It is quite clear from his results, as it had been from those of Rashbass and Rushton with a long electrode thrust below the sheath, that the latter is, in fact, a very significant barrier.

In the light of the above it is inevitable that the views of Lorente de Nó should be treated with reserve. He rejected the concept that the membrane might contain pores, and that substances might therefore influence permeability, but considered that a substance may modify nerve function without necessarily penetrating the fibres (a view very much in accordance with the metabolic concepts of Quastel, which will be described later). Throughout his books (167,168) there is a heavy emphasis upon metabolic effects. Metabolism must supply energy required for the performance of nerve function and must maintain the integrity of the nerve processes, although he was aware that the two activities may be independent of each other. From his own experimental work he concluded that the nerve impulse depends only indirectly upon respiration, although the resting membrane potential depends upon oxidative metabolism, and the nerve impulse cannot be produced unless the potential is raised above a certain level. He regarded the nerve impulse as the result of changes in the nerve fibre which establish new electromotive forces rather than causing the brief disappearance of the existing resting ones. This alteration cannot be

produced unless the resting membrane potential is above the critical excitability level, and he admitted that lack of sodium ions or anaesthetics of the cocaine type may prevent the production of the alteration without lowering the resting membrane potential. This last is an important admission. It is evident from his work that there is no general conformity to the mechanisms which he postulated, especially as he further claimed that, in all essential respects, the action potential changes induced by temperature reduction are identical with those produced by oxygen lack or by depolarizing agents.

The work of Lorente de Nó associated with the acetylcholine theory of nerve transmission is considerably more significant, since this drug has influenced a certain amount of local anaesthetic research. This hypothesis, stemming from earlier work by Calabro (38) and Bergami (13), was that acetylcholine may be responsible for the propagation of the nerve impulse along the axon. Nachmansohn (197,198) expressed this theory by claiming that acetylcholine is released, from an unknown precursor, by a flow of current from the inactive regions of the nerve. This current is set up by the local circuits provoked by the spike potential: the acetylcholine depolarizes the membrane and a new local circuit is established which, in its turn, excites neighbouring regions. The acetylcholine is immediately destroyed by cholinesterase, and is re-synthesized during the recovery period by the enzyme choline acetylase: it is then combined with an inactive precursor, ready for release when the nerve is stimul-

-ated again. Nachmansohn also extended the concept to muscle transmission.

Acetylcholine can be extracted from many types of nerve in different species, and choline acetylase can be found associa--ted with nervous tissue (Grundfest, 96), but experiments by Bronk (29) and Lorente de Nó (166), showed that substitution of sodium by acetylcholine in the external medium, in concen--trations ranging from 0.01% up to isotonic, produces no effect. In this work eserine was used to protect the acetyl--choline: later, (167) Lorente de Nó asserted that the eser--ine had, in fact, protected the nerves against the destruc--tive action of acetylcholine. Without eserine acetylcholine chloride at concentrations greater than 0.5 - 1% gave irreve--rsible depolarization, irrespective of the pH of the soluti--on. In the earlier paper he claimed that even in massive concentrations acetylcholine does not depolarize nerve fibres as it does end-plate regions or ganglionic synapses, whilst in his 1947 one he found that at sub-depolarization concentra--tions peripheral nerve is very insensitive to the presence of acetycholine in the external medium: in fact, isotonic acetylcholine has been successfully used as an indifferent medium for nerve recovery after depolarization produced by an excess of potassium ions. The importance of eserine to the two sets of results is very striking as acetylcholine alone in massive concentrations does not prevent conduction of impulses until it has produced an irreversible deteriora--tion of the nerve fibres, whilst in the presence of anticho--linesterase it does not prevent conduction of impulses at any time. He suggested that the former might be caused by the enzymatic hydrolysis of /

acetylcholine producing a toxic substance. Acetylcholine forms choline and acetate, and as choline is known to be non-toxic, acetate is highly suspect: in fact, acetate is known to have a deleterious effect in certain concentrations, and Lorente de Nó proceeded to the suggestion that this might explain why the acetylcholine effect is only obtained with quite large doses.

In 1947 also, Toman et al(273), from their studies of the effects of D.F.P. upon acetylcholine actions concluded that ...."acetylcholine plays no importance.... in the conduction of the impulse."

Despite this, and other contradictory evidence, Nachmansohn continued to assert the validity of his theory. In his appraisal of the theory, Feldberg (57) stated that Dale's words of 1948 are still true....."The ingenuity of its (the theory) supporters is sorely taxed to discover even plausible ways of escape from the facts which contradict it." Nevertheless, Feldberg agreed with Nachmansohn that both nerve and muscle contain relatively high concentrations of cholinesterase: in his opinion the function of this enzyme here is unknown and only provides grounds for speculation.

When examining the excitability of a single nerve fibre in a nerve trunk Lussier and Rushton (174) noted the distortion caused by the epineurium, and confirmed that, when this is removed, the excitability corresponds with the simple cable theory of Cremer. However, when nodes of Ranvier were involved another picture was apparent. This immediately suggests

a connection with the saltatory theory of nerve conduction which was advanced by Erlanger and Blair (55). It proposed that the impulse is not transmitted along the nerve at a uniform rate, but in a jumping (saltatory) fashion, each segment between two nodes of Ranvier behaving as a unit. The axon is excited at a node, and the whole internodal segment is activated. This restriction of excitability to the nodes has been frequently confirmed (136,265a,265b). von Muralt (285) maintained that the excitable membrane is not disposed longitudinally on the outer surface of the axon, but trans--versely at each node. However, no proof has been forthcom--ing that this membrane is depolarized at the passage of an impulse and that it is re-polarized during the recovery peri--od.

Lorente de Nó (167) observed saltation of impulses across a nerve block created by crushing, provided the block was not more than 1 - 1½mm. wide: with cocaine the area involved is normally too wide for jumping. As far as the saltatory theory itself was concerned, he was unable to accept it, des--pite further support for it from the work of Tasaki and his colleagues (264,268).

Two years later, Rashbass and Rushton (213) envisaged that the impulses pass quickly along myelinated sections of nerve and receive a "boost" at the nodes. Huxley and Stämpfli (127) endorsed the concept of saltation: they regarded myelin as a conductor functioning to increase conduction velocity by making local circuits act at considerable distances ahead of

the active region. This view is favoured by the fact that agents producing stimulation or depression of conduction have a stronger action at the nodes than on the internodes. (Sanders and Whitteridge (227) have demonstrated that, in fact, conduction velocity is related to the diameter of the myelin sheath and not to the internodal length.) From their evidence they supposed that the action potential process is generated at the nodes of Ranvier. In keeping with this they found that blocking an internode stops the impulse, presumably due to interruption of current flowing forward in the axis cylinder and back in the fluid of the myelin sheath. A similar arrangement seems to apply for unmyelinated fibres since the nerve conduction rate can be reduced if it is raised into the air to decrease the volume of the surrounding fluid.

An important piece of work was done by Katz (138) on the depolarization of sensory terminals and the initiation of impulses in the frog muscle spindle. He found that stretching depolarizes sensory nerve endings, and a local potential change can be recorded from the afferent axon at a point close to the spindle. The potential change varies with the rate and amplitude of stretching, and gives rise to repetitive impulses in the sensory nerve. He reported that depolarization increases with velocity of stretching until it attains a maximal value.

Katz also indicated a difference between frog and crustacean nerve inasmuch as the latter shows much less shift in

depolarization level. He attributed this to the two changes involved in recovery after conduction:- 1) A restoration of the membrane resistance, 2) A gradual return of "excitabil--ity". The existence of the two different processes had been indicated by Hodgkin (115). Katz emphasized that the link between the two factors is not yet known, and that they may depend upon different mechanisms: moreover, they may not proceed at identical rates, or even at the same relative rates in different tissues. If membrane leakage repairs were considerably quicker than the return of excitability, then a larger depolarization would be required before the following impulse of a series could be initiated. If, how--ever, both recovery processes occurred at approximately the same rate, or the second were faster, then all the impulses would be generated at practically the same depolarization level, as is found in Carcinus axon, and hence its differ--ence from frog nerve.

Katz reported a good"off" effect in the muscle spindle. When he used procaine he found that, in the absence of sensory impulses, the positive change was obtained, i.e. it is not necessarily an after-effect of nerve activity. The mechanism responsible for this effect is difficult to under--stand, unless it is caused by some anomalous action of pro--caine.

On analysing the stretch he discovered two phases. The first, coinciding with the period of initial lengthening, is a relatively intense effect, due, he suggested, to changes in membrane capacity. The second is a static

effect, during which the local depolarization and rate of dis-
-charge are maintained at a lower level, which may be due to
a change in membrane permeability. The mechanism is specula-
-tive, but he firmly believed in the existence of the two phases
of the response. Hakansson (98) has lately confirmed the ex-
-istence of membrane changes upon stretching.

By 1951 the trend towards a focus on membrane effects was
so firmly established that Albert (4) wrote...."the cellular
membrane is now recognized as playing an essential rôle in
the propagation of excitation, hence it is a likely site for
the action of hypnotics". This thought was especially inspi-
-red by the fact that the hypnotics do not act as depressants
when injected into cells, but only when allowed to act from
outside.

From the foregoing it is evident that the question of im-
-pulse transmission is not entirely straightforward. Likewise,
when transmission is applied to sensation, the picture is not
a simple one. Intensity of stimulation of receptors has to
be expressed, and this can be done by frequency of impulses
(2).

If all sensation were equally anaesthetized the problem
would be greatly simplified. This is not the case, hence
the query put forward by Whitteridge (295) arises, as to
whether some lines are preferentially paralysed. Moreover,
the same author has shown (294) that some receptors are anae-
-sthetized, whereas others are sensitized, e.g. trichloroe-

-thylene gives rapid shallow breathing which may be due to the sensitization of deflation endings, whilst volatile anae--sthetics produce an impulse rate from pulmonary stretch receptors which is about double that produced by the same volume of air.

From such observations, although they refer specifically to general anaesthetics, one can deduce that the problem of anaesthetic action is likely to be extremely complex.

THEORIES OF GENERAL ANAESTHESIA, AND THEIR RELEVANCE TO LOCAL ANAESTHESIA.

In 1799 Sir Humphry Davy suggested the use of nitrous oxide for general anaesthesia, but it was not until 1844 that it was used for operations. In 1846 ether was first used on human beings, to be followed by chloroform in 1847. These drugs were known to have depressant actions upon the central nervous system, but it was not until the turn of the cent--ury that the first theory of the mode of action was formula--ted. It was introduced, almost simultaneously, by Overton and by H. H. Meyer, and it is therefore termed the Overton-Meyer hypothesis. Various other theories followed it.

1. The Overton-Meyer Theory.

The first essays in this field appear to have been made by Bibra and Harless in 1847 (20) using the depressant drugs ether, acetic ether, and ethyl chloride, on dogs and on frogs. They noted the solvent properties of these drugs, and sugges--ted that the cause of narcosis is the dissolving of some fa--tty constituents of the brain, which are re-deposited in

the liver. An immediate criticism of this idea is that it fails to account for the reversible effect of the anaesthet--ics, unless one concedes that there is either some rapid re-synthesis of the fatty constituents, or a re-transferr--ence of the original ones from the liver back to the brain.

Nevertheless, their theory aroused interest in the relat-ionship between fatty constituents and anaesthesia. In 1908 Reicher (221) demonstrated that, during chloroform anaesth--esia, there is an increase of fat in the blood stream: it is unfortunate that the drug he selected should be one which affects fat metabolism (in cases of delayed chloroform pois--oning there is commonly a fatty degeneration of the heart and liver.)

The term"lipoid" was coined by Overton (202) to cover the true fats, and also the more elaborate fat-like substances, such as lecithin and cholesterol. The use of such complex substances presented difficulties in analytical research as it proved impossible to employ brain tissue, or even the extracted and denatured brain lipoids: consequently, a simp--le model substance was often employed, the original (and favourite) one being olive oil.

The basic concept was to relate anaesthetic activity of a drug to its partition coefficient, making use of this model. It is relevant to note here that both local and general anaesthetics are, as a rule more soluble in fat than in water (91). On the same lines, Burger (36) main--tained that the theories of nerve penetration used in dis-

-cussions of general anaesthesia hold also for preferen-
-tial penetration of lipoid nervous tissue by local anaesthe-
-tics, although he did not think that the theories of general anaesthesia explain the mechanism of local anaesthetic action. (Underlining by the writer). It is noteworthy that the commonest known local anaesthetics are alkaloids, and that the alkaloidal bases are all highly lipoid soluble.

The full theory, endorsed by Overton, was published in 1899 by Meyer (186). Three concepts were involved:-

1. All chemically indifferent bodies which are lipoid sol-
-uble must act as narcotics to living protoplasm in so far as they can become distributed within it.
2. They must act first and most markedly in those cells in whose chemical structure these fat-like substances predominate (and form peculiarly essential participants in the cell function.)
3. The relative degrees of activity of such narcotics must depend on their mechanical affinity for the fat-like substances on one hand, and for the other constituents of the body, e. g. water, on the other. Consequently, they depend on the partition coefficient which deter-
-mines their distribution in the mixture of water and lipoids.

The theory leans heavily on Overton's concept that the essen-
-tial constituent of the cell wall is lipide.

Later, Meyer (187) attempted to elaborate the first concept, and to show that solution in lipoids not only forms the mech-
-anism by which narcotics enter the cell, but is the cause of narcosis itself. He believed that the presence of the

narcotic in the lipoid "loosens" their connections with other cell constituents, and that it also increases the permeability of the cell wall, thus disturbing ionic and other equilibria.

Toman (272) was cautious about the theory because the critical lipide phase of neurones is relatively unknown, either as regards its electrical properties or its affinities for narcotics, and because many anaesthetics and groups of anaesthetic agents fail to conform to it. His conclusion was largely derived from the work of Löfgren (165) who measured the distribution coefficients of several local anaesthetics with a water and oleyl alcohol model. This model had been introduced by K. H. Meyer and Hemmi (190) as a better representation of the cellular lipides involved in narcosis, and their experiments on tadpole narcosis seemed to support this view. Lofgren concluded that local and general anaesthetics are not strictly comparable, and that the theory might have some validity for the latter.

In 1936 an attempt was made to define the shortcomings of the theory (188). It was suggested, a) that all inhibitions are not attributable to the same mechanism, i. e. different drugs may act at different primary points and bring about the end-results (of depression) in a variety of ways, b) that the lipide theory is only applicable to the "indifferent narcotics" or the "alcohol group" (an ill-defined group of fat-soluble organic compounds, of which alcohol and chloroform are typical members), c) that the further a drug is

removed from its group, the more its mechanism of action might be expected to deviate from the theoretical one. These propositions obviously limit the theory, and also admit the possibility of exceptions to it.

Adriani (3) considered that the theory is acceptable even though it is most applicable to the aliphatic compounds and it fails to give an indication of the partition between blood and brain (which is the vital functional one).

From the literature it seems that various workers have attempted to apply the concept too rigidly with a model which was largely chosen for convenience. (Brink and Posternak (28) have reported the correlations between activities and various physical properties, but emphasized that this does not sign--ify that they are important to the mechanism of narcosis). Moreover, Butler (37) stated that determination of the distri--bution coefficient is sometimes technically difficult, and consequently many published results are probably seriously wrong.

Collander (42) studied the distribution of numerous compounds between water and various organic solvents, and commented that in membranes the lipide molecules are orientated in layers, whilst in bulk phases (as in models) they are rand--omly distributed, and could therefore behave quite differ--ently. He doubted if there is any theoretical advantage in studying coefficients with solvents that are chemically more closely related to the membrane than is olive oil.

Obviously, cell constitution is immensely important in the application of this theory. All cells have a definite structure: protoplasm is an aqueous solution which is sep--arated from the outside environment by a plasma membrane, and therefore any substance passing into a cell must pene--trate this membrane. Work and Work (299) have stated that, in some cases, the degree of correlation between lipoid solubility and penetrant powers of a drug is most noteworthy, but stressed that some lipoid insoluble substances may penetrate into cells, and also that species differences exist. They did not preclude the theory because of this, but suggested that there are two possibilities for membrane structure, firstly a continuous lipoprotein skin, or secondly, a sieve-like structure. Overton, on the other hand, inter--preted the penetration by lipoid-insoluble substances as indicating the existence of an active transfer mechanism (203).

Burger (36) admitted that the true anaesthetic is preferentially absorbed by cells containing large amounts of lipide, but argued that the composition of nervous tiss--ues invalidates the theory, since only half of the solids are lipides, whilst up to 90% of the total of the nerve consists of water. This argument is ludicrous. Nerve may merely contain about 5% of lipide, but, even if there was only one hundreth of this amount present, there is no rea--son why it should not govern anaesthetic action, provided that it is situated at strategic positions for producing block.

From the assumption that drugs produce narcosis by dissolving in the fatty parts of nervous tissue, Barlow (9) concluded that:-

1). All chemically inert substances which are fat-soluble must exert a narcotic action.

2). This effect appears first, and is most marked, in cells in which fatty substances play a major part.

3). The potency of a narcotic agent will depend upon its re-lative affinity for the fatty tissue in the presence of body fluids.

His basic assumption is most questionable, and his first conclusion is definitely untenable, but a further concept is much more acceptable, namely, that drugs have to penetrate the neurilemma, hence fat solubility may be necessary for the entry of a drug into the axon, i. e. it is concerned with a step in a chain of depressant events rather than being the means of depression itself.

Earlier, Butler (37) had remarked that, for anaesthesia to be feasible the anaesthetic agent must penetrate to its site of action in a very short time. For this reason he did not reject theories of anaesthesia based upon physical proper-ties: he considered that properties allowing access to a site, and those producing actions at a site must have some common ground. Hansteen (101), however, maintained that lipoid solubility and penetration are not related as it still occurs in lipoids which have been denatured: he therefore favoured some sort of adsorption effect involving the lipoids.

If local anaesthetics do act intracellularly with the cell constituents, then the dissociation constants could be an important consideration in defining anaesthetic activity (88), provided the right models are found. Failure to imitate cell membrane lipoids, e. g. cholesterol, may be the cause of the anomalous drugs which have high partition coefficients but are not depressants (4). Various attempts have been made to rectify this (141, 189,190), but with only limited success. Indeed, Gerard (81) commented that the relationship between effective concentration and distribution coefficient, althou--gh theoretically interesting, does not bear close examinat--ion.

It is worth remarking that substances with partition coe--fficients which are too low to confer depressant properties often have strong analeptic ones. Pharmacologically this is not surprising, as even chemically similar drugs may possess widely divergent properties.

Some attempts to relate molecular structure to lipoid solubility have been made (165, 191), but the results do not extend to local anaesthetics.

When applying the Overton-Meyer theory to local anaesthe--sia, Bennett and Chinburg (12) believed that the cell membrane is the probable site of action of these drugs. Their studies of the axon surface, however, failed to yield any further evidence affecting the hypothesis.

Supporting evidence for the theory came from Gros (94), Jumikura (133), and the work of Adams et al. (1) on the anaesthetization of goldfish.

However, Löfgren in 1948 (165) stated that it was impossible to draw any conclusions of even approximate accuracy on the basis of the data in the existing literature, because the experiments recorded had, in some way or other, been inadequately performed.

In his own experiments especial care was taken to maintain pH constancy. He found that various general narcotics may also work as local anaesthetics, when they probably conform with the Overton-Meyer rule: with his own local anaesthetic compounds he concluded that the minimum effective concentrations of these drugs cannot be a function of the distribution coefficient alone.

The importance of his results must not be underestimated lest it be thought that he may have used anomalous compounds it should be noted that from amongst them came lignocaine, whose local anaesthetic efficacy is undisputed.

However, he did not reject the Overton-Meyer rule completely, and he reported experiments to support the view that local anaesthetics behave ideally in the lipoid phase.

From this Butler (37) made the far-reaching, but inevitable, suggestion, that physical properties might merely be a factor regulating the access of the drug to its site of action.

Skou (250e.f) carried this concept further. Using local anaesthetics and extracts of nerve lipoids from desheathed frog sciatic nerve, he concluded that a correlation exists between anaesthetic potency and penetration of a monolayer of nerve lipoids. Like Löfgren, he was careful to use a

constant pH in his experiments, since it can play an import--ant part in local anaesthetic activity.

An extreme evolution of the theory was provided by Höber (113), who suggested that special lipoids have particular functions, in which case there is little point in determin--ing coefficients with a mixture extracted from an organ as has frequently been done. He advanced the idea that the collapse of the membrane following stimulation is due to the breakdown of the structural lipoid, and that this can be inhibited by charging it (the lipoid) with narcotic. The heavy emphasis on lipoid membrane constituents does not appear to be justified.

When considering the theory it must be stressed that the authors made it clear that it was based on a simple model for convenience, but this has frequently been disregarded. Other models have yielded better correlations, e. g. oleyl alcohol for general anaesthetics (165), and lecithin in gela--tin for local anaesthetics (133).

The strict interpretation of the theory immediately creates difficulties since all fat soluble substances are obviously not narcotics, and it also fails to explain why some drugs with normal (37) or 'sub-depressant' (4) partition coefficients behave in an opposite fashion i. e. are convul--sants: it is tempting to presume that inadequate lipoid pene--tration, with consequent accumulation outside the tissue, is the cause, especially in view of the more recent demonstration (217,218) of a direct relationship between the ability

of many substances to penetrate cellular barriers and their oil-water coefficients, independent of their molecular weights.

The theory assumes that lipoid is an essential cell constituent of nervous tissue. Its presence seems to be certain (47,251), although the fatty myelin may represent a complication.

Dawes (47) obviously accepted the theory when he referred to increased lipoid solubility being associated with both in--creased quinidine-like, and local anaesthetic, activity. However, some hesitancy about the relationship for local anaesthesia is natural, and Löfgren's rejection of its rigid interpetation, because compounds with the same coefficients may possess widely differing activities, is very understand--able.

Finally, careful note should be made of:- 1) Traube's admission (278) that lipoid content of brain cells must influence his surface tension theory, 2) The contention (101) that denatured lipoid behaves like the normal substance, he--nce adsorption is the salient feature, 3) The belief, ex--pressed by Meyer himself (187), that the presence of the narcotic in the lipoid changes the permeability of the cell wall.

Clearly, a link exists between this and other factors.

2. The Traube hypothesis.

The basis of the theory is that the drug causes a change in the surface tension of the cell. Traube (274) noticed that substances which lower surface tension pass most rapidly

into the cell, and concluded that this effect must be an important measure of their ability to pass the cell membrane. He observed that amongst these substances are many narcotics, and that narcotic strength and surface activity (adsorbability) are related in a fashion similar to narcotic strength and lipoid solubility: this could be expressed quantitatively in a homologous series of compounds.

The theory was formulated in two papers (275, 276). Traube suggested that the more a drug lowers the surface tension, the less likely it is to cling to the surface, and this inverse relationship could be measured by its capillary activity at an air/water interface.

That Traube cannot have been fully satisfied with the theory per se is apparent, because he later indicated (278) that air/water interfaces may differ from water/lipoid ones: while strongly water soluble narcotics depend for their penetration on capillary activity, the true narcotics are more dependent upon the presence of lipoids.

Henderson (110) observed that, despite this, there is a better agreement between capillary activity and narcotic concentration than between comparable figures based on the Overton-Meyer theory. Sexton (235), on the other hand, quoted Hurst's belief (126) that the Overton-Meyer and Traube hypotheses can be reconciled by taking into account more specific characters which influence molecular interaction in monolayers. Gerard, (81) and Skou, too (250c.d) had similar views.

Commenting upon Traube's hypothesis, Toman (272) suggested that, despite wide adoption of the concept, it has not been subjected to rigorous test. This seems to be a fair criticism.

Pribram (210) quantitatively studied the effect of local anaesthetics on water surface tension. Despite the finding that pharmacologically inactive substances exist which have more surface tension lowering activity than procaine, he still concluded that local anaesthetic activity is related to this property.

Albert (4) emphasized that air/water interface results are only applicable to members of homologous drug series, and they merely signify the non-wettability of the substance, and do not imply any specific adsorbability on a cellular recep--tor.

Benedict et al. (11) used a series of procaine analogues and found a general correlation between surface tension eff--ect and local anaesthetic activity in goldfish. Miescher (193) reported a direct relationship between the two in alkaline solutions of dibucaine homologues, and cautiously concluded that lowering of surface tension may be one of many factors influencing anaesthetic properties.

As alkalization increases the surface activity of alkaloi--ds Traube (277) attributed the increased potency of local anaesthetics in alkaline solution to this cause. Luduena et al. (173) used various local anaesthetics, including procaine, cocaine, and lignocaine, and noted a lowered surface tension: with lignocaine alkalization produced an even lower surface

tension, and increased potency. Their various attempts to correlate surface activity and local anaesthetic potency were largely unsuccessful.

It is obvious that adsorption is deeply involved in the Traube theory. Indeed, Henderson (110) remarked that the importance of the theory lies in its connection with the adsorption one. Its links with permeability and penetration are also clear, but the review by Buchi in 1952 (33) on the relationship between physico-chemical properties and local anaesthetic activity, reported that research has yielded conflicting results about the surface tension correlation.

Local anaesthetics may lower surface tension in vitro (3), but it has been maintained (156) that many good narcot--ics do not lower the interfacial tension between oil and water. Results from water must be treated with caution in view of the contention (278) that the clinging intensities of narcotics to lipoids and to water are often completely opposite. Correlations are obtainable, but the significant ones have always been derived from homologous series of drugs (4, 167,173).

Moreover, some substances lower the interfacial tension between oil and water, e. g. soaps and detergents, but have no narcotic properties (81).

Finally, the observation (165) that chloroform and lignocaine increased the surface tension of an ergosterol film model completely contradicts the theory, but this may be due to the model chosen. In fact, the choice of model gives rise to considerable doubt about many facets of this theory.

3, The Warburg Theory.

Narcotics are readily adsorbed on surfaces in vitro, and a similar adsorption may occur at the cell surface.

The first suggestion of such an action was made in 1909 by Lillie (159). Later, Warburg (287) showed that narcotics could displace amino acid from a charcoal surface. He related the phenomenon to surface action, stating that narcosis is determined by the number of the adsorbed molecules on one hand, and the surface covered by each molecule on the other: it is independent of the chemical nature of the narcotic.

Langmuir (150) suggested the molecules may act in adsorption membranes as multimolecular layers. If this is true it weakens the whole theory, because the formation of a unimolecular layer was a basic assumption for the hypothesis.

Henderson (110) observed that all the models used in examining this theory dealt with enzymatic effects, chiefly oxidation ones: this is especially important as he was convinced that narcosis and depression of oxidation are not the same thing.

The work of King et al. (141) linked the Warburg theory with the Overton-Meyer one. In a quantitative investigation of the latter, using water and paraffin oil, they calculated the actual number of molecules adsorbed at the interface, and the area occupied by them. Their results (with a homologous series of compounds) appeared to indicate that the more a drug is adsorbed at the body interfaces between tissues, the stronger will be its narcotic action.

The addition of lecithin produced irregularities: this is probably explicable by the complex nature of lecithin and its hydrolysis products. Despite this, Hirschfelder and Bieter (111) regarded lecithin and kephalin as being most important cellular compounds for increasing the action of narcotic drugs.

Other experiments on similar models were performed by Seel--ich (234), and by Tammelin and Löfgren (cited by Löfgren 165).

Löfgren suggested that, in vivo, the anaesthetic tends to be distributed in the cell lipoids, but is strongly retarded in the phase boundary (he actually stipulated at the node surface) because of high viscosity: a highly concentrated layer of anaesthetic therefore forms near the phase boundary, and when it has reached a certain concentration the disturb--ance of the membrane film may reach the anaesthetic stage. He admitted that the view of a surface disturbance is includ--ed in both the Traube and Warburg theories, but he claimed that their presumption, that the narcotic is adsorbed at the membrane surface due to its surface activity, was wrong, and that it is inapplicable to simple hydrocarbons.

Two further objections were raised by Höber (113). Firstly, there are substances which produce narcosis without being adsorbable (as far as is known) upon any cell structure or constituent, and there are substances which are exactly the opposite. Secondly, in homologous series, other distribution phenomena as well as adsorption are significant, and cannot be disregarded.

He mentioned the increased paralysing effect of alkaloids

with rising pH, as compared with threshold concentrations of the alcohols being independent of it, and those of the barbi--turic acids actually decreasing with a pH increase. This, he maintained, agrees with both the lipoid and the adsorption theories, as the (active) undissociated base in--creases at the higher pH values, and Rous and Drury (224) had shown that the undissociated compounds are more adsorbable and lipoid-soluble than the ionized salts. Earlier, Rider (220) had claimed that the intact local anaesthetic salt is adsorbed by nerve cells, possibly by structures of a lipoid nature. This further marriage of the theories requires no comment.

Finally, Höber et al.(114) in 1939 advanced the theory that small concentrations of narcotics prevent the spread of nerve impulses by their high surface activity: the adsorption layer protects the surface film of the nerve from chemical and physico-chemical changes which are essential features of the excitatory process, i.e. it produces some sort of membrane stabilization. Although referring to adsorption, this concept provides a very real link between the accepted views on nerve transmission and the next (permeability) theory of narcosis.

In adjudging the Warburg theory it is likely that adsorp--tion can potentially influence two processes. Firstly, it may decrease metabolism by "blanketing" oxidative processes, and, secondly it may affect permeability by decreasing poro--sity.

The first type of effect has been disputed by Henderson (110). A greater electrical resistance in narcotized than in normal

nerve has been shown (97), and other authors have demonstrat--ed that this is accompanied by an increasing resistance to the passage of solutes, thus lending support to the second mechanism.

In fact, both processes are covered by other theories, so the present problem is the investigation of adsorption alone, in which case the doubts raised by various authors (113,150, 165) cannot be overlooked.

That this theory, like others already examined, does not fit all drugs having anaesthetic properities (or even local anaesthetic ones) is extremely significant. Adsorption, by itself, is unlikely to explain anaesthetic action.

4. The permeability theory.

The basis of this theory is that, as normal nervous excita--tion involves molecular changes of the nerve membrane (in--cluding increased permeability to ions) a substance which can stabilize the membrane will prevent these changes, thus producing a conduction-blocking effect.

Höber (112) was the first to suggest that adsorption of an anaesthetic decreases the penetrability of the cell. This was supported by Lillie (159,160) using Arbacia eggs, and in a later paper (162) he set out the theory in the terms indicated.

At about the same time membrane stabilization by narcotics was reported by Lepeshkin (157) using the root hairs of Trianea and the giant cells of Tradescantia, and also by Lange and Kappus (149) from experiments on muscle: the

observation by the latter workers that narcotized muscle may show increased or decreased permeability is a complete enigma, although it may have been related to the substances chosen for experimentation.

Winterstein (297) considered that narcotics decrease natural permeability, but specified adsorption as being the means of achieving it. He considered that some, but not all, of this adsorption occurs in the cell lipoids. (Both Höber and Lillie also regarded the presence of lipoids as being of more than just casual importance). He obviously attributed the changes to a blanketing effect of adsorbed molecules similar to that envisaged for the inhibition of oxidative metabolism (211).

Lillie, too, (162) envisaged narcotic adsorption on, foll--owed perhaps by dissolution in, the membrane, and he stress--ed the electrical changes which accompany the membrane stab--ilization. Once the change is produced in the cell it is narcotized, and no penetration of ions, salts, or water is required, i.e. the theory is one of a change in the physical state of the membrane.

Subsequent investigations have failed to support the concept of a universal permeability-decreasing effect of narcotics, but Butler (37) emphasized that the theory only concerns permeability changes associated with excitation, and any other type is irrelevant. It is questionable as to how far this argument can be taken, but there is certainly a real danger in trying to transfer results obtained from

one type of tissue or drug into generalizations about other ones, and this fact cannot be overlooked.

Although the theory was advanced for the central nervous system, peripheral nerve fibres furnish more accessible objects in which to study the effects of drugs on polarized membranes. In them the blocking of impulse transmission by stabilizing the depolarizing process has been sufficiently demonstrated to convince Butler that there may be some found--ation to Lillie's theory.

Höber et al (114) studied the influence of various organic substances on the resting potential of muscle and nerve. They concluded that cytolytic agents increase the characteristic spacing in its surface film structure so much that normal selective cation permeability is lost, and all ions can pass through, i.e. the polarized state is lost, but it can be restored when the agent is removed, thus allowing the origi--nal structure to be re-arranged. They considered that narco--tics act by cytolysis, provided they are given in effective (narcotic) concentrations.

In his book, Höber was more specific about the permeabil--ity changes (113). He stipulated that interfacially-active narcotics are adsorbed to the structures in which the excit--atory process occurs, and this prevents the complex reactions accompanying narcosis from taking place. The important change is a decrease in permeability to ions, but he admitted that other solutes and water may be involved. He envisaged that the narcotics may form an adsorption layer upon the pore walls and, by narrowing the aperture in this way, obstruct,

or even completely block, the passage of substances through the channels, so that even small molecules, e. g. water, may be prevented from entering.

Hirschfelder and Bieter (111) noted that action current in nerve is accompanied by an increase in permeability, and stated that, whether the surface is regarded as a continous layer of lipoid, or as a sieve-like mosaic with narrow chann--els running through the lipoid phase, evidence exists that anaesthetic drugs decrease the permeability of the surface layer.

Observing block without depolarization, Bennett and Chin--burg (12) were "forced" to the view that anaesthetics fix cell membrane conditions and prevent the phasic shifts ass--ociated with conduction: the prevention of the calcium-in--duced shift in resting potential by pre-treatment with pro--caine, strongly supports this opinion.

Gerard (81) believed that narcotics variously affect perm--eability. He admitted, however, that permeability might determine the entry of an agent into a cell without account--ing for its action inside. This idea naturally assumes that increase in permeability is required for a favourable nar--cotic effect and this contradicts the theory. However, there is a possibility that his (unqualified) definition of narcotics may not include local anaesthetics.

Nevertheless, his concept of permeability relating to drug entry is a far-reaching one, supposing as it does that the theory explains a phase, rather than the complete mechanism,

of narcosis. He used general anaesthetic drugs to arrive at this conclusion, whereas Lorente de Nó, although omitting details of his rejection of the theory (167), almost certain--ly used cocaine (and possibly other local anaesthetics as well).

Consistent support for the theory has come from Shanes, and a recent comprehensive publication (243) merits closer scrutiny. He based his work on the hypothesis, derived from the modified Bernstein theory, that the membrane potential is a consequence of the selective permeability characteris--tics of the membrane, and of the concentrations of the ions bathing the extracellular and intracellular surfaces. He recognized the importance of metabolism in ionic movement, designating it "active transport", but he did not believe that it contributes directly to membrane potential.

His view of permeability restriction is far removed from a surface-clogging effect. He noted that two types of model membrane have been studied, a) the oil or non-aqueous solvent type, in which ion penetration is governed by the distribut--ion coefficient and related properties, b) the rigid porous type, like collodion. He visualized the ions in the porous type as passing through channels whose diameters in places are near to those of the hydrated ions: cation and anion velocities can be controlled by altering the charge on the channel walls, thus a net negative charge makes the membrane selectively permeable to cations, and vice versa.
Mullins (196) suggested that ionic entry into membrane pores involves a solvation (interaction with membrane constituents)

with the pore walls, making larger as well as smaller pores inaccessible to the ions, but Shanes discounted this.

Shanes regarded the membrane as a semi-rigid, semi-fluid, structure, with lipide molecules held together by intermole-
-cular forces. He felt that the contribution of protein to rigidity at aqueous interfaces is limited, in view of the observation (40) that large oil droplets can "snap" into cells (Arbacia eggs) without being constricted, and membrane continuity is then re-established.

He prescribed some flexibility in membrane molecule spacing, depending on orientation, inroads by foreign molecules and ions, changes in intermolecular forces, and temperature.

As in earlier papers (237,238) he envisaged two classes of active substances, the stabilizers and the labilizers. The former (including calcium, procaine, cocaine) reduce the electrical effectiveness of sodium, potassium and other ions, whilst the latter (including low calcium, veratine) accentuate the ionic effects on membrane potential. He defined stabilizers as agents blocking nerve or muscle impulses without any change in resting potential. They show conduction block, lowered excitability, and, in pharmacolog-
-ically-active concentrations, they have no effect on the inter-pore regions.

He conceived that such agents act on the inter-pore regions. The stabilizers "dissolve" by molecular displace-
-ment, and thereby increase lateral pressure on the pores, so decreasing channel size and permeability: the last pre-

-vents depolarization on stimulation. He conceded that deve-
-lopment of a solvation might affect the energy barrier to entry.

About labilizers he was indefinite, suggesting that they may reduce lateral pressure by adsorption on interchannel regions rather than by being dissolved in them. The labilizing action of veratrine is an interesting concept, because if it does, in fact, destroy permeability, then penetration should be vastly accelerated.

At all events, Shanes' concept of stabilization harmonizes with observed results in the light of Hodgkin's description of nerve transmission (117).

Early evidence of stabilization affecting ion permeability came from muscle experiments (236): these swelled in Ringer where part of the sodium was replaced by potassium (Boyle and Conway (26) had shown that the swelling is proportional to KCl entry). Cocaine reduced the entry, and exposure to KCl indicated a reduction in its normal depolarizing effect. Sh-
-anes extended the work to other local anaesthetics and anti-
-histaminics (239) with similar results. His work on potass-
-ium leakage in potassium-free solution indicated a stabili-
-zation effect by cocaine (240), and Holland and Dunn confir-
-med this in guinea-pig auricle (125).

Prior to this, Hardt and Fleckenstein showed that prevention of depolarization by various stabilizers is accompanied by potassium retention (102): sodium was not investigated. There is no evidence of any differential effects, and certainly so-
-dium and potassium are equally affected.

Local anaesthetics in roughly blocking concentrations had little effect on conductance of single medullated fibres

(232), and Tasaki (267) reported that a significant decrease only appears with concentrations greater than blocking ones. Shanes suggested that there is a low concentration effect, predominantly on sodium permeability, which contributes little to membrane conductance, but raises its potential, while higher concentrations affect the more important contri--bution of potassium to conductance.

The theory raises the important factor of rate of action. It partly depends on the speed of arrival at the site of action in the nerve fibre, but could also be influenced if physiologically-active substances are emerging from the channels but cannot escape, and hence accumulate around the fibres. This may occur even in single fibres, unless they are well irrigated (243).

In nerve transmission ions are an important factor, but Straub (261) has shown that the hyperpolarization from low sodium, or the depolarization by excess sodium can be de--pressed by both cocaine and procaine. Direct measurements of sodium and potassium using cocaine on toad sciatic nerve 241,242) and squid giant axon (244,245) led Shanes to suggest that:- a) Cocaine depresses free ion movement only, and not other types of transfer, b) The effects are limited to the outermost layer, c) This effect layer is below the one in the fibre where sodium enters and is carried out again, because cocaine does not interfere with active exclusion, but prevents external sodium entering the membrane when active transport is blocked.

This implies that at least one enzyme system related to sodium exclusion is situated at the outermost surface of the cell.

That excess calcium decreases potassium and sodium perm-eability, whilst reduction of calcium increases both has been confirmed by Frankenhaeuser and Hodgkin (71). The latter effect has been effectively stabilized by cocaine (256) and partially so by 0.05 mM of procaine or less: Straub (261) considered that the last is geared to the pH (see also 245) and added that stabilizer charge may be important in potassium permeability because procaine is more effective in depressing potassium depolarization at low pH...." at which the anaesthetic is largely a cation."

It has been proposed that normal and experimentally-induced changes in membrane potential are due to modifications in the calcification of the fibre surface, but as the characteristic membrane effect of local anaesthetics is still exerted in the absence of external calcium, Shanes felt it would be difficult to demonstrate, although he admitted that intracellular calcium might be important.
Shanes believed that calcium and low temperature produce stabilization, not by lateral pressure on the pores, but by increased rigidity of the inter-pore region: this reduces flexibility, and hence permeability, of the membrane.
Finally, any weakness or lack of effect of stabilizers generally might be due to inability of the channels to be further compressed.

The various aspects of this theory have been developed

at some length here, because the concept is obviously very pertinent in the light of present knowledge of impulse tran--smission.

5. The colloid and protein coagulation theories.

Bernard (16) showed that cell colloids may aggregate during anaesthesia, and that this process is reversible. Observing reversible rigidity of frog muscle he conceived the view that narcosis consists of a reversible semi-coagu--lation of the substance of the nerve cell. These two observations led to the formulation of two related concepts of anaesthesia, the colloid and protein coagulation theories They are considered in turn.

Bancroft and Richter (8) claimed that narcosis is a non-specific action (just as simple surface adsorption is), due to a change in the colloidal dispersion of protoplasmic com--ponents. They claimed that stability of colloidal suspen--sions of both proteins and lipoids, as observed under the ultramicroscope, is reversibly affected, and they regarded the effect on the proteins as being of equal significance with that on the lipoids.

Their work has been criticized by Hirschfelder and Bieter (111) because it was done under unusual conditions.

Barlow (9) significantly observed that, a)Narcotic con--centrations of anaesthetic are much smaller than those need--ed to flocculate the colloids, b) Coagulation is a toxic effect and is irreversible, c) In some cases narcotics apparently decrease the dispersion of colloids. Consequen-

-tly, he rejected the theory completely.

Butler (37) regarded the colloid theory as the product of over-simplification and a tendency to discount the complex--ity of living systems, hence its expression in terms of simple physicochemical change. This criticism seems to be justifiable.

Regarding the protein coagulation theory, Moore and Roaf (195) found a reversible opalescence with 1% chloroform added to blood serum: beyond 2% an irreversible precipita--tion occurred. (In 1881 Salkowski (226) deomonstrated that chloroform in narcotic quantities in the blood stream pro--duced no precipitation, even after months).

From such evidence Henderson (110) presumed that the toxic effects of high concentrations of narcotics may be attribut--able to precipitation intra-cellularly, or at the cell sur--face. This seems to be drawing a very thin line between this and the full precipitation events which occur, for ex--ample, in rigor mortis.

Another aspect of this topic is synergism. Shillito (247) demonstrated a marked potentiation of local anaesthetics by the addition of egg albumen and gliadin, and this was con--firmed by Schmidt (228). Stender and Amsler (258), using rabbit cornea, found a potentiation with fresh egg white, but none with guinea-pig or rabbit serum, gelatin, or traga--canth: the serum results are disappointing. Sollman(255) showed that various soluble anaesthetics can precipitate, or at least cause opalescence, in serum, but this appears

to have no functional significance.

The two theories are so similar that joint criticism is justified. Neither has much supporting evidence, and neither would appear to allow the speedy reversibility characteristic of local anaesthesia. The synergisms are interesting, but no conclusions about mode of action can be drawn from them.

There is no alternative, therefore, but to conclude that, though colloid or protein coagulation may be produced by general or local anaesthetics, there is no evidence to suggest that the manifestations are in any way associated with the mechanisms of narcosis.

6. The dehydration theory.

Dubois (50) suggested that anaesthesia is caused by water loss from the cell or cells concerned, due to the anaesthetic, but he was unable to prove that it was reversible. Kochmann (143) considered that anaesthetics reversibly dehydrate or stabilize the cell colloids, and thus reduce membrane permeability, which leads to metabolic inhibition and functional arrest, i.e. narcosis. Winterstein (297) disputed this, on the grounds that dehydrated muscle can become very irritable.

The evidence for this theory is bald and unconvincing, and fails to substantiate the concept (111) that the action potential is accompanied by dehydration changes in certain areas of the nerve. As a theory of general anaesthesia, let alone local anaesthesia, it is quite unacceptable as it stands.

7. Acetylcholine theories.

The origin of these is difficult to trace. The concept of

acetylcholine activity in nerve transmission is nowadays discredited (see p.18), but its rôle in autonomic transmiss--ion is undisputed. As local anaesthetics may act on all forms of nerves it is apparent that this topic must be con--sidered.

Much evidence has been obtained from muscle preparations: this does not preclude it, but it must be treated with reser--ve.

Wilson and Wright (296) claimed that procaine inhibits acetylcholine release at the neuromuscular junction, and this was endorsed by Harvey (105) and Jaco and Wood (129): Harvey also (104) asserted that the neuromuscular action of procaine differs from its direct action on muscle.

Thimann (269), however, concluded that procaine and similar local anaesthetics block the acetylcholine receptors at sensory nerve endings. This view of a competitive action was also held by Nicholls and Quilliam (199), who indicated its parallel in d-tubocurarine.

The link between local anaesthetic activity and anticho--linergic effects has often been noted (48,52, 272), and Elio remarked upon the local anaesthetic effect of atropine, claiming that it is about 50% that of procaine. Both he and Peczenik and West (206) concluded that these drugs exhibit substrate competition with acetylcholine. However, the latter authors emphasized that some results are not so con--clusive as they initially appear. For example, Elio's local anaesthetics were anticholinergic in the skeletal and plain

muscle tested, but rabbit cardiac muscle yielded extremely divergent results. (The possibility that tissue differences could explain the anomalies should not be overlooked.) From rat diaphragm preparations they further inferred that local anaesthetics and d-tubocurarine act differently, or at different parts of the neuromuscular mechanism.

Procaine appears to antagonize decamethonium block (53), but potentiates that of succinylcholine (69). The latter may be due to competition for plasma cholinesterase, which hydrolyses both compounds (85, 134). Assuming that procaine is, in fact, anticholinergic, the above contradicts Bovet's suggestion (25) that succinylcholine block is produced by acting like an excess of acetylcholine. Yet again, succiny--lcholine may compete with procaine for the enzyme, thereby causing acetylcholine accumulation, and hence block. It is clear that no predictions can easily be made.

Foldes et al. (69) found no direct antagonism between procaine and succinylcholine clinically, but it was evident in cats and dogs, perhaps due to their naturally low choline--sterase levels (6), or to lessened competition for the enzyme. If the former is correct, species difference must be appro--ached extremely cautiously, and cannot be under-rated. Work by Ellis et al. (54) suggests that the second possibil--ity is of minor importance.

Earlier, Tobias et al. (270) had tested the actions of several narcotics, and found that none of them inhibited cholinesterase at all. This was contrary to the conclusions formed by Payot (204) with surface-active local anaesthetics,

including cocaine, upon erythrocyte cholinesterase: Grieg et al. (93) endorsed this, but not for drugs like procaine which are inactive upon surface application.

The involvement of esterases in local anaesthesia was propounded by Bieter (21) because D.F.P. and eserine can abolish conduction without depolarization or transient excitation. Toman et al.(273) noted that they, and procaine, block conduction, raise the threshold, and lengthen conduction time to as much as double the normal in frog sciatic nerve. They attributed conduction failure without depolarization with all these drugs to an increase of the threshold above a critical value, although the Nachmansohn theory demands that anticholinesterases should produce an enduring nerve depolarization.

Although threshold elevation is probably important in local anaesthetic action (272), the implication that hyperpolarization is a factor because of the antagonism from the supposed depolarizing agents (67,200) has received little further support.

Toman et al. suggested that the nerve blocking is due to side-effects which are independent of anticholinesterase activity: large doses of D. F.P. are needed to give block, whilst relatively low concentrations antagonize cholinesterase. As eserine shows no consistent local anaesthetic properties (93,167, 271) these can hardly be due in practice to inhibition of either cholinesterase. Furthermore, all anticholinesterases do not act on nerve like these two: such discrepancies would not occur if acetylcholine accumulation

is the basis of conduction block.

Grieg et al (93) stressed the question of penetration. Some local anaesthetics are very active upon mucous surfaces, e.g. butacaine, while others are inactive e.g. procaine. They attributed this to permeability differences linked with inhibition of cholinesterase activity, as seen in erythrocy--tes. They claimed that surface active compounds penetrate the mucous membrane by inhibiting cholinesterase, while the inactive ones (e. g. procaine) can produce anaesthesia if the enzyme is first blocked by eserine. They anticipated the obvious criticism by showing that eserine by itself had no effect.

A question of locus of action arises here. Eserine prod--uces block in nerves of frog and other species: Grieg et al. acknowledged the species problem, but used the cornea of rabbit as a subject material. This is frequently used for quantitative work, but less often for studying modes of action, so the results must be treated with some reserve in case of "tissue differences".

Grieg and his colleagues had to assume that eserine in--creases the permeability of optic mucous surfaces: as it had been shown in erythrocytes they experienced no difficulty in doing this. Secondly, they assumed that penetration is related to cholinesterase inhibition.
Their concept, despite its assumptions, has by no means been discredited (9), although it must demand high cholinesterase levels in, or near, nerves in order to produce preferential effects upon nervous tissue.

In 1956 Kalow and Maykut (135) examined the interaction between cholinesterases and a series of local anaesthetics, and concluded that the drugs have a greater affinity for serum cholinesterase than for other enzyme systems so far investigated. (The full significance of the last 3 words should not be lost.) They used homologous compounds to minimize errors, such as different diffusion and detoxica--tion rates. This limitation of the field creates some apprehension about the general applicability of their resu--lts. They claimed that the affinity between enzyme and anaesthetic rises with increasing length of side chain of the latter, but failed to get a linear correlation between local anaesthetic potency and affinity for either body cholinesterase.

Skou (252 a,b.) studies local anaesthetics in the electric eel, and concluded that cholinesterase inhibition is not correlated with peripheral nerve blockade.

Bülbring (34) confirmed that both atropine and cocaine depress the isolated rat phrenic nerve-diaphragm preparation. She affirmed Brown's theory (30) that atropine interferes with acetylcholine liberation rather than competing with it like curarine, and that procaine is very similar to atropine. Harvey (104) reached similar conclusions with the cervical sympathetic ganglion.

However, Sinha (249) rejected the suggestion that atropine activity and local anaesthetic effect are similar. In all his comprehensive studies he also noted that procaine seem--ed to play a lone rôle, and this observation may be signi-

-ficant. Dawes (47) conceived that procaine consists of two dissimilar molecular species, which might explain its complex action at neuromuscular junctions.

In summing up this section it is clear that evidence from the action of anticholinesterases further confirms the reje--ction of the acetylcholine theory of nerve transmission. In the autonomic nervous system little evidence is at pres--ent available from the synapse, though this field might be informative. With neuromuscular junctions results are obta--inable that local anaesthetics are curariform, but there is no general agreement that the modes of attaining block are similar. That such effects may be side reactions is far from improbable, especially in view of the fact that the in vivo use of local anaesthetics does not produce any ob-vious autonomic or neuromuscular effects. Finally, the possi--bility that cholinesterase may, in some way, be linked with penetration is an interesting one, and should merit further investigation.

8. The histamine theory.

It is debatable if this ranks as a theory, but a brief men--tion of it is desirable. v.Euler (282) showed that many nerves contain histamine, and it has been suggested that it participates in nervous conduction (a view which has failed to gain acceptance).

Toman (272) noted that histamine may relieve procaine block: although ascribed to an acidity effect he claimed that it is independent of pH, thus local anaesthetics must be essentia--lly antihistaminic.

Certainly the reverse is true, as many antihistaminic drugs show local anaesthetic activity, e. g. mepyramine (48). However, Sinha (249) studied the antihistaminic properties of local anaesthetics and concluded that the two activities are not related.

As, therefore, the relationship seems to be fortuitous, further consideration is unnecessary.

9. Ionic influence.

The influence of ions has never been raised to the status of a theory, but the current views on nerve transmission suggest that ions are potentially very important.

Potassium chloride can stimulate nerve, but large doses produce a powerful blocking effect which can synergize with doses of local anaesthetics (205), although procaine may yield contrary results. Straub (260) noted that potassium depression can be antagonized by eserine and neostigmine, whereas Whitteridge (295) has indicated that potassium ions can increase excitability to a limited extent: this apparent duality of potassium should be borne in mind.

Jéquier et al.(1) suggested that potassium and glucose metabolism might be related: this may not be so unlikely as it appears, as Hodgkin (117) concluded that the intake of potassium, at least, is metabolically controlled. From his own work, and that of Handler (100), Gerard found strong indications that gluconeogenesis is increased by narcotics (81), and this might be associated with the same processes.

Sinha (249) studied the local anaesthetic inhibition of

KCl stimulation in various tissues. He concluded that KCl inhibition values are far nearer the relative anaesthetic activities than are the anticholinergic ones. The full com--plexity of these "inter-relationships" is seen in the pot--assium loss in mammalian heart during vagal stimulation, i.e. linked with acetylcholine release (243), and the incre--ased potassium movement in sinus venosus fibres with low concentrations of the ester and vagal stimulation (19), the effects being abolished by atropine (103). Present evidence is limited to the heart, but the claim (90) that pressure causes electrolyte disturbances in the skin similar to acet--ylcholine injections is more pertinent, especially when con--sidered in conjunction with pressure blocking effects.

Potassium studies probably evolved from local anaesthetic synergisms: the empirical surgical use of potassium sulphate with cocaine and procaine has long been practiced.
Hoffman and Kochman (124) demonstrated a species difference effect with equivalent strength mixtures of local anaesthe--tics and potassium sulphate injected intravenously into guinea-pigs and intradermally in man: the former were less toxic.
Adriani significantly observed (3) that pain and oedema after injection limit the usefulness of potassium potentia--tion. Other authors have stressed the irritant effect of potentiating compounds (284,258).

Berger (14) claimed that magnesium sulphate is more potent than the potassium salt, but Hirschfelder and Bieter (111) refuted this: they considered that potassium increas--es the permeability of the surface, thus facilitating the

entrance of the local anaesthetic. (This concept is not fully convincing, as the local anaesthetic action on permeability might directly antagonize the potassium action). It is interesting that synergisms of caffeine with amydricaine, theobromine with cocaine, and methylene blue with procaine (163, 155) have been reported: both caffeine and theobromine increase the permeability of most body membranes, whilst methylene blue has metabolic effects.

Kochmann and Hurtz (144) reported that morphine synergizes with the motor block of cocaine: this may indicate that sensory block was already maximal, hence no further potentiation was possible. Sollman and Estable (256) used KCl and suggested that the anion effect may be important, as it increased cocaine and procaine motor, but not sensory, blocks. This curious result may spring from the respective ratios of the compounds concerned (220), or from a circumstance similar to the morphine synergism. This emphasis on anions contradicts the earlier practices in which the cation was regarded as the important synergizing factor.

Rider (220) systematically investigated synergisms, especially that of butacaine and other local anaesthetics: in many ways it behaves like an inorganic substance, although it too, is capable of being synergized by potassium sulphate. He surmised that potentiation is due to the chloride ion, largely because butacaine hydrochloride is more active than the sulphate. That one local anaesthetic may behave like an inorganic substance towards other drugs seems quite anomalous. Subsequently Rider introduced the important consideration of effects of solubility differences. Butacaine hydrochlo-

-ride is less soluble than the sulphate: he visualized that when two drugs are in contact with nerve cells, the less soluble one will tend to escape from water to any structure capable of receiving it. Moreover, the presence of abundant body chloride may hinder sulphate because it may have to be adsorbed first, and lose activity in so doing. This rôle of body chloride is important, because it creates the possibil--ity that a drug may have completely different modes of ac--tion in vitro and in vivo. This leads on to the whole field of pH effects, whether due to body constituents or to extern--al manipulations.

Some most important experiments were performed by Bishop (23) on frog sciatic nerve, using KCl and cocaine as block--ing agents. He claimed that some depressant agents may block nerve and muscle without depolarizing them, and he inferred that depolarization (depression of potential) occuring with some depressants is not necessarily a cause of block, but rather one of the external signs of the con--dition produced. He considered that block is due to a raising of the threshold for excitation tantamount to a con--dition of persistent refractoriness. The action potential conducts at full amplitude until an impulse of normal inten--sity cannot stimulate the adjacent segment of nerve, hence excitation is interrupted. He noted that the course of depression by various agents is strikingly uniform, and conduction block occurs at about the same decremental value with all of them. He surmised, therefore, that they act at the same/

place in the reaction chain constituting nervous activity, or that depression of potential is one of the last links in a chain, and these agents may act at various preceding steps in the process. He believed that the second was more likely.

Bein (10) claimed that optimal cell functioning depends on ionic ratios, especially of potassium and calcium, rather than on absolute amounts. However, he quoted evidence (7,86) that the absolute concentration of potassium is important for some drug actions.

Both potassium and calcium alone produced variable or indeter-minate effects, but with procaine and electrolyte combina-tions the two ions appeared to be antagonistic. Bein decided that, in local anaesthesia, absolute amounts of potassium and calcium are sometimes more important than the ratios between them. This illustrates how easily an effect can be modified, the difference here being between the ion effects in normal and procaine-treated cells.

Bennett and Chinburg (12) used isolated frog nerve to confirm Bishop's concept of conduction block without depolarization. They did this from the study of action and resting potentials with fourteen local anaesthetic substances. The report, by Höber et al. (114) of depolarization with procaine and cocaine was considered to be due to the use of excessive concentrations far beyond the needs of conduction block: the concentration used was double that of Bishop, and seven times stronger than that used by the authors to produce 90% block in frog nerve. Moreover, many of Höber's results came from crab, and as it is more sensitive to drugs than

frog nerve, Bennett and Chinburg assumed that the discrepancy of results may be even greater still.

They considered that several anaesthetics, applied in sufficiently high concentrations over long periods, will depolarize nerve. (Bishop, too, had recognized such exceptions.) They claimed that such observations, without corresponding data on degree of block and duration of drug application (Höber et al. gave neither) reveal nothing of the mechanism of block. They associated the increased resting potential in incomplete anaesthesia with a decreased rate of re-establishment of normal relations about the less permeable membrane, and thought that the last explains why many anaesthetics block high frequency impulses before complete conduction block begins. The importance of this is potentially great in view of present concepts of nerve impulse frequencies (2,89,138, 295).

Lorente de Nó (167) observed that excess of magnesium ions slightly increased the threshold of nerve stimulation, but exerted no narcotic effect. On the other hand, excess of calcium ions caused irreversible deterioration of the nerve fibres, and, peculiarly, damaged the rapidly-conducting A fibres more than the C ones. Histological evidence revealed that the myelin sheaths of the former were swollen and irregularly broken. He ascribed this to penetration and accumulation of calcium ions in the myelin: osmosis produces swelling and disintegration of the myelin layer, thus destroying its conduction faculties. He alleged that excess of potassium has similar effects.

Shanes (237, 238) considered that the negative after-potential is partially due to the depolarization caused by potassium excess in the vicinity of the fibre surface, whether it be crab or squid. Thus, stabilizers, which de--crease permeability, restrict potassium loss and reduce the after- potential. He attributed the potential to inadequacy of the metabolic processes. Gasser (75) suggested that aft--er-potentials are signs of recovery processes following impulse conduction, but Lorente de Nó claimed to have found them in areas which have not been activated: he therefore doubted their value, even though he reported that anoxia decreases them , while post-anoxically they are potentiated. Actually, the last observation may support the concept of an oxidative recovery mechanism which is active after impulse conduction. The claim that the potentials can occur in in--active nerves could seriously contradict Shanes, if it were confirmed, but he emphasized that permeability changes are more important than metabolic ones in governing the movements of ions across the membrane.

Katz (138) demonstrated that stretching a muscle depola--rizes its sensory nerve endings: this creates a local potential which generates the sensory impulses. Procaine elimi--nates the spike and after-potential without affecting the depolarizing effect of stretching. This confirms Bishop's concept of block without depolarization effect. The spike disappeared in gradual stages which could be related to

anaesthetic dosage. Sodium-free solutions gave similar effects.

Toman (272) noted that, paradoxically, cocaine transiently restores conduction in a sodium-free medium. However, Lorente de Nó (170) had shown that it summates with partial sodium lack to abolish conduction. Some sort of dual effect of sodium, similar to that shown by potassium, is not impossible.

McDowall and Soliman (183) suggested that many drugs produce sodium accumulation at specific receptors, but as they used Kreb's solution instead of Ringer's their results are not strictly comparable with others. In the light of present knowledge about transmission this effect might be expected if the action of the drug is to bring about membrane stabilization: this affects permeability, and hence the movement of sodium inwards at excitation.

10. Metabolic theories.

The concept that narcosis may involve metabolic changes, enzymatic or otherwise, is not new. Verworn (280,281) diverted attention from the physical concepts previously held. He suggested that narcotics interfere with cell oxidations, and that anaesthesia is essentially a type of asphyxia caused by a loose union between the anaesthetic and the oxygen-carrying groups in the cell.

Contrarily it has been observed that narcotics, in effective concentrations, do not decrease oxygen consumption, e. g.

in sea urchin eggs, and that, in some cases, oxygen uptake may even be increased, as when alcohol acts on the spinal cord (297,298).

Nevertheless, Warburg (286) showed that narcotics inhibit the oxidation of amino acids and similar substances. He ob--tained (288), from charcoal models, results indicating that the larger the individual molecule, the fewer are needed to coat a given surface and to produce inactivation of catalysis (and hence inhibition).
The choice of model and substrates cast some doubt on the cogency of the conclusions.

Quastel (211) demonstrated that anaesthetic concentrations of narcotics reversibly inhibit the oxygen consumption of brain slices. This was true for the oxidation of glucose, lactate, or pyruvate substrates, but not for succinate ones. This enigma still remains (262). The validity of results obtained from such preparations and applied to general anaes--thesia has been questioned (167), but, despite this, Quastel's concept has been widely accepted.

Watts (289) tested local anaesthetics on brain substrates. Unlike Quastel's central narcotics, they inhibited succinate oxidation. Cinchocaine was the most effective compound, and cocaine and procaine the least effective ones. Watts conc--luded that these drugs protect the anaerobic glycolytic en--zyme system.

Earlier, Sherif (246) investigated various anaesthetics on isolated rabbit sciatic nerve: cocaine and procaine both reduced oxidation, and the effect increased with concentration.

The most powerful agent for reducing metabolism was eucupin--otoxin, but it has a negligible effect on nerve conduction. 5% urethane was roughly equivalent to 2% procaine. Sherif believed that urethane affects nerve oxidations in relatively high concentrations only, though it has a marked effect on the oxidation processes of brain tissue (164). This idea is an important one, suggesting as it does a difference in reaction in the two types of nervous tissue: it keeps recu--rring.
Unfortunately, Sherif did not examine the conductivity of nerves, so its relationship to chemical phenomena was not formulated.

Bishop (23) noted, that cocaine hydrochloride quickly renders nerve inexcitable, but has no definite effect on the resting potential of respiring nerve. Lorente de Nó (167) maintained that, nevertheless, cocaine inhibits the metabolic processes related to the maintenance of the resting potential because it delays the anoxic depolarization, and the oxida--tive re-polarization, of nerve. It is now clear that there is some truth about the latter, but evidence for the former is not decisive. As cocaine itself does not depolarize resting nerve (at least for several hours) Lorente de Nó surmised that it prevents membrane depolarization and decreases a number of metabolic processes in such a way that the normal membrane potential is maintained with a reduced oxygen consumption. In 1912 Verwörn (281) had suggested an effect on certain respiratory chains might occur without any

overall respiratory changes. Gerard, also (81) declared that functional anaesthesia is not always attended by depressed respiration.

In a study of conduction block, Lorente de Nó observed that cocaine produces very little change in electrical properties, whilst they are profoundly affected by ether. This suggests a major fundamental difference between the two types of drug. He rated oxidative metabolism more highly than any ionic concentration in maintaining membrane potential: he recognized the importance of sodium and potassium ions only as much as they directly or indirectly participate in enzymatic reactions.

Gerard (81) felt that narcotics probably act along oxidation-inhibition lines, but noted that, in general, the most convincing evidence for interference with cell metabolism is obtained with more complicated systems rather than with simpler ones. Consequently, much information has accrued about suspected locations of block in various systems, whilst more fundamental considerations may have been omitted.

Kalow and Maykut (135) suggested that local anaesthetics inhibit dehydrogenase in the cytochrome complex. However, Michaelis and Quastel (192) stated, from work with chloretone, that this link is not narcotic sensitive; they suggested a blocking of the main oxidation chain, narcotic action being limited to cytochrome b or to an intervening flavoprotein.

Grieg (92a,b) endorsed this, whereas Watts (289) with local anaesthetics, traced it down to cytochrome c. Butler (37) invoked evidence of a negative kind, viz. that it does not occur at other steps, hence the links cited above might be involved.

Gerard stressed the limitation to all this work in that the site of action was determined by exclusion rather than by positive proof. He suggested that narcotics might inhibit complete systems (but not their fragments) by some relatively non-specific physicochemical action, rather than by blocking a postulated link. The work of Johnson and his co-workers (131,132) may bear this out and suggests plurality of modes of action: in luminous bacteria ether narcosis denatures the enzyme proteins, whereas with barbiturates such a change is not involved.

Gerard's views were not shared by others. Burger in 1951 (36) favoured the idea of the high susceptibility of nervous tissue to oxygen lack, and declared that differences in metab--olism are involved. He claimed that a susceptible link is a carrier between dehydrogenase and cytochrome oxidase, but tacitly admitted that it may not be the only one affected. Barlow (9) suggested a parallel between local anaesthetic potency and inhibition of succinate metabolism. To support the idea of enzyme inhibition he mentioned speed of onset, emphasizing that an enzyme would be probably affected instant--aneously by drugs.
Speed of action would thus be basically controlled by rate of penetration into the axon, and might account for the different

rates of various local anaesthetic effects. Albert (4) too, postulated a drug accumulation in the membrane producing dis--organization of enzyme sequences.

Much work on enzymes has utilized models or simple mixtures of enzyme and narcotic. The drawback to this, and related, research, is that it is certain that even the complete tissue in vitro may behave very differently from the same material in vivo. Barlow cited some narcotics which, in vitro, low--ered creatine phosphate and raised inorganic phosphate levels, whilst in vivo they had exactly the opposite effect. Presumably the basic physiological difference between nervous tissue in vivo and in vitro is that the former is still activ--ely working. McIlwain (184) devised a method of electrical stimulation of cerebral cortex slices in vitro, and found that the levels of metabolic activity were then the same as in similar tissue in vivo. This technique may prove useful in further research, but could well be more applicable to the brain than to peripheral nerve.
Potassium stimulation has also been used to overcome the diff--erence, and, with cerebral cortex slices thus treated, it is claimed that some local anaesthetics can depress respiration (79).

Butler (37) acknowledged enzymatic inhibition, but indicat--ed that neither it, nor the inhibition of brain tissue oxy--gen consumption, are effects peculiar to anaesthetics. In--deed, some inhibitors are convulsants e.g. picrotoxin, metra--zol, and Butler regarded the inability of the theory to

explain the difference between anaesthetics and convulsants as a serious deficiency. He also discounted the idea (212), using cocaine as a narcotic, that although the oxidation rate for the whole brain might show little change, small areas may suffer from oxygen shortage. Such a concept would be very difficult to prove satisfactorily.

Although he rejected inhibition of oxidation as the cause of narcosis, Butler observed that it often accompanies anæs-thesia. In the intact brain this might be due to a reduction in the number of neuronal discharges which occur continously, and which, naturally, consume oxygen in their recovery phases.

Experiments on autonomic ganglionic synapses by Larrabee (partly in 151, partly in personal communication to Butler) revealed block with narcotic concentrations less than those needed to measurably decrease oxygen consumption. Despite the tissue used they made Butler doubt if decreased oxygen consump-tion is the cause of brain synaptic block either. In this tissue, the synaptic block mechanism still remains unknown (41)

Larrabee et al. (152) used drugs in concentrations suffic-ient to block sympathetic transmission. Sodium pentobarbit-one reduced resting metabolism, even in concentrations less than synaptic blocking ones: moreover, the concentration had to be raised 5-10 times to block B and C fibres. (This re-emphasizes the pitfall of tissue differences, and even of different systems of the same type of tissue.) Ethyl alcohol also reduced resting metabolism: cocaine produced block in concentrations equivalent to depressive ones of the barbitur-

-ate, and yet, even with 5 times this concentration, it failed to depress resting metabolism. The conclusion is unmistakable, and especially significant in its demonstration of a divergence of metabolic effects between general and loc--al anaesthetics.

With sympathetic ganglia an interesting feature was re--vealed when Larrabee et. al. (153) obtained block and depress--ed oxygen consumption with pentobarbitone or chloretone: methylene blue administration restored the oxygen consumption level, but not transmission. Cyanide, however, reduced the resting rate of oxygen consumption considerably before de--pressing transmission, and depressed the extra oxygen consumption of activity more than the activity itself: this suggests that there is some sort of reserve which permits some degree of anaerobic activity.
They finally concluded that anaesthetic block is not due to interference with oxygen consumption.

Due to Quastel, much of the work on metabolism has dealt with oxygen utilization. However, inhibition of other mechanisms is a distinct possibility. Butler (37) noted that most of the quasi "narcotic" drugs can inhibit the breakdown of adenosine triphosphate, even in disrupted or dead cells. He emphasized how little is known of the effects of anaesth--etics upon phosphate metabolism: this is given further point by the claim (117) that clear evidence exists that A.T.P. is probably the energy source for sodium ion extrusion. Caldwell

and Keynes (39) made it quantitative by suggesting that 4 phosphate bonds are broken for each sodium ion ejected. Whit--tam (293) has recently concluded, from studies of various substances, including potassium and A. T.P., on human red blood cells, that the second may be linked with active cation transport. Sutcliffe and Hackett (263) considered that a phosphorylation mechanism can explain ion transport under both aerobic and anaerobic conditions. This trend is both new and important, as previously hesitancy had been felt about applying results from muscle energy relationships to nerve.

Another potentially important metabolic topic is the cit--ric acid cycle. Using rat brain and various local anaesth--etics (including cinchocaine, procaine, lignocaine, and cocaine) Ryman and Walsh (225) reported an inhibition of ci--trate synthesis, the more potent compounds having the better inhibitory effects. No supporting observations are yet available.

Butler considered that very few pharmacological effects could surely be attributed to a direct action of a drug on a known enzyme, and that general anaesthesia is not among them. From much of the information cited above it appears that local anaesthesia is still further removed from such a mechanism.

Nevertheless, the importance of metabolism cannot be ig--nored, because, regardless of the specific processes invol--ved, the continuous expenditure of energy is necessary for at least part of the resting potential (238). This is

linked with the maintenance of the ionic states inside and out-
-side the nerve. If interference with metabolism occurs it
must ultimately influence the ionic state, and hence the con-
-ductivity. Conversely, if conditions in the nerve are altered
it is likely that metabolic conditions will also be influenced.

From crab Shanes decided that invertebrate nerve block results in depolarization caused by metabolic inhibition, but he stressed that the blocking mechanism may differ in frog fibres. Certainly, it seems that crab fibres have enzyme sys-
-tems which are fairly sensitive to local anaesthetic agents, but whether this is the mechanism underlying block or not, the species effect is again very apparent.

In considering the theory, one of the foremost questions is whether the work done against the steady ionic leak of nerve is aerobic or not. Hodgkin and Huxley (120) believed that anoxia can arrest recovery processes, and Wright (300) con-
-cluded that oxygen lack, and narcotics, produce depolarizat-
-ion, but produce differing effects on nerve thresholds. Lorente de Nó reported that anoxia alone does not totally depolarize, hence metabolism only depends indirectly upon respiration. His concept of an oxidised material reserve seems reasonable, as there is an equivalent in muscle: it seems to be more typical of peripheral nerve, and might create the impression of partial respiratory independence. This could explain why brain may be very susceptible to oxy-
-gen lack, whilst it is conjectural if peripheral nerve is similarly affected (153).

11. Electrical theories.

Since electrical events are involved in excitation it is not surprising that theories of this type have been propounded. Burge (see 3), reporting a change in polarity of fish brain cells from electro-negative to electro-positive, attributed this physical change to the action of drugs. Erlanger and Blair (56) had similar views. Since potassium, sodium and chloride ions carry the electrical charges in nerve (117,167), any change in ion distribution will show accompanying electr--ical changes, and thus Burge may have observed the effect, rather than the cause, of block.

A different approach is the production of narcosis by electrical currents themselves (81). In 1859 Pflüger (209) had noted that an applied cathodal current lowers, and an anodal one raises, the threshold of stimulation of the nerve, although on removal of the current the situation may be rever--sed. Lorente de Nó (167) however, claimed that cathodal de--pression can occur, and he attributed this in some way to temperature, a view which has received no further substantia--tion. The "block" is reinforced by rhythmic activity of the nerve: single impulses may pass the block, but it will prev--ent conduction of trains of them. Anodal block, on the other hand, prevents conduction of single volleys of impulses, and may even break down if the nerve is made to conduct a rhythmic train of impulses (56). Of the two, cocaine is more similar to cathodal block, especially as it may produce "partial" block of high frequency impulses. There, however, the simil--arity ends, if Lorente de Nó is correct in his contention that cathodal block is due to a progressive depolarization of the nerve membrane.

It has been claimed (167) that electrotonic effects can be used to distinguish the modes of action of some narcotic drugs, but this still awaits further substantiation.

It is questionable how far the electrical approach can be taken. The passage of electrical currents may change excita--bility, but this is not a practical method of local anaesth--esia. Bishop (23) maintained that nerve block is not prima--rily due to altered potentials, but to altered irritability. He had earlier claimed (106) that deviation of the absolute refractory period is one of the most delicate indices of the condition of the nerve: this is debatable, but the observa--tion of electrical conditions, e.g. membrane resting poten--tial and action potential, can furnish important information about the events caused by local anaesthetics, rather than b--eing regarded as a means of explaining modes of action.

12. Thermodynamic theories.

(Thermodynamic activity is an estimate of the work per mole--cule required to transfer the narcotic from the pure liquid phase to the unknown one of locus of action in the narcotiz--ed cell, and is derived from vapour pressure determinations).

The theory was first set out by Ferguson in 1939 (60), and Albert later (4) expressed the conviction that the deg--ree of hypnotic and anaesthetic action of general anaesth--etics in mammalian nervous systems is governed by Ferguson's Principle. The word "degree" is important, as the principle applies more to potential efficacy of a drug than to its mode of action.

Ferguson reasoned that narcotic actions depend on a physical mechanism governed by the equilibrium between the concentration of the drug in the external and its concentra--tion in the affected phase. He claimed that if a particular pharmacological effect depends on a 'physical' mechanism, the thermodynamic activities of drugs producing this effect should lie in a narrow range, variation being due to secondary effects related to the chemical structure of the drug. Any major deviation would indicate a 'chemical' rather than a physical action.

Brink and Posternak(28) proposed the use of thermodynamic activity as a measure of narcotic effectiveness. Using syna--pses of cat stellate ganglion, they concluded that the concept of equal narcotic effect at equal thermodynamic activities is more generally applicable than Ferguson thought. This was especially true in cell oil phases, but they did not regard this as denoting that narcosis occurs in some oil phase of the cell. They considered that narcotic effectiveness is due to molecular cohesion, and that these drugs act in regions of the cell into which they can fit. From this it is clear just how much of a physical concept underlies the whole theory. They rejected any idea that chemical constitution can vary effects.

In other animals they deduced that a cause of deviation from the 'rules' might lie in differences in cell structures responsible for the narcotic effect (i.e. tissue differences) and assumed that other factors as well might conceal the eff--ects considerably in whole organisms.

Two of their observations are noteworthy:- a) In luminescent bacteria the rule only applied in alcohol series to those with 10 carbon atoms or less. b) Ether often fails to conform to the rule, although as a surgical anaesthetic there is nothing exceptional about it.

They clearly recognized that thermodynamic methods of analysis will not reveal molecular mechanisms of narcosis, although these are intimately associated with modes of action.

Butler (37) commented that anaesthetic activity is not always determined entirely by physical properties (although it might suffice for some drugs e. g. alcohols). In fact, no anaesthetics show regular relationships between their pot--ency and any physical property, hence physical measurement not only fails to predict anaesthetic doses quantitatively, but also fails to predict reliably the qualitative nature of the pharmacological action.

Nevertheless, the association is something positive, and the fact that many anaesthetic drugs are recoverable unchanged suggests physical rather than chemical effects, although it does not preclude their participation in some reversible reaction.

Toman, too,(272) considered the results to be inconclusive, although allowing a comparison of narcotic activities based on a simply measured physical property.

Barlow (9) felt that the difficulty of choosing between the various theories of general anaesthesia had been largely "over--come" by using chemical potential (obtained from liquid or

vapour phases) as an activity index, instead of concentration in oleic acid or at charcoal surfaces. There is a great difference between an activity index and an explanation of mode of action, and even Brink and Posternak (28) have admit--ted that the theory cannot fulfil the latter.

Evidently, classing this as a theory of anaesthetic action is a misnomer. Like electrical activity, thermodynamic stud--ies may be useful for predictions and observations of behav--iour and effect, but they do not clarify the means of action of local anaesthetics at all.

OTHER FACTORS IN LOCAL ANAESTHESIA.

Several topics are closely related to the present problem. They include pH effects, differential effects, and structure-property relationships.

a. Effects of pH.

Investigations of pH have often provided information about the active form of local anaesthetics, whilst the study of the latter has frequently been governed by the pH. It is not considered desireable to divorce such information here, since the two are so evidently inter-related.

Bignon in 1892 (22) showed that alkalization increases the activity of cocaine solutions, and introduced a milky alkalized suspension of cocaine ("cocaine milk") into clinical practice: its activity was, in fact, very little greater than normal cocaine hydrochloride. Gros (94) attributed this to the formation of coarse particles which diminish the amount of active free surface. He confirmed Bignon's observations with other local anaesthetics, including procaine and amy-

-locaine. Later (95) he suggested that the greater potency in alkaline solutions is caused by the free base being the only active constituent: alkalization potentiates anaesthesia due to the increased amount of base liberated. Other authors (100,111, 220) have supported this view. He suggested that the free bases of all anaesthetics have much the same activity, and that a correlation exists between local anaesthetic act--ion and the solubility of tne base in the lipoid solvents. The former has been strongly criticized by Löfgren (165). Sollman (253, 254) showed that sodium bicarbonate increases the motor efficiency of cocaine and procaine about 8-fold on motor fibres and 2-4 times on sensory fibres, of isolated nerve. He suggested that the alkali helps the liberated anae-sthetic base to penetrate into the nerve trunk. Bieter (21) has criticized these results.

Régnier and David (214) considered that all the aqueous fo--rms of cocaine (ions, base, and salt) are active, and that the alkali acts directly on the tissues concerned, because the addition of alkali to a saturated aqueous solution of cocaine base increased its anaesthetic action. Trevan and Boock (279) explained this result thus: very little cocaine base is necessary to produce anaesthesia, but its buffering action is negligible, hence the body tissues can effectively oppose its action by forming a salt with it. When alkali is added the pH is raised, and less cocaine combines with the anions of the tissue, hence more of the active base can affect the nerve fibres. Further proof lay in the fact that variations

of pH from 5-8 have no influence on the anaesthetic activity of benzyl alcohol, a neutral anaesthetic, on the cornea. They tested most of the compounds used by Gros, and corroborated the theory that the base is the only active fraction. (The free base itself is sparingly soluble, hence the use of soluble salts.).

In later papers (215, 216) Régnier and David investigated the potentiation of cocaine, procaine, and various procaine salts, and still concluded that release of the free base plays a minor part only in the phenomenon, as compared with the direct effect of the alkali.

In 1931 Gerlough (83) noted that the presence of acid seems to inhibit local anaesthesia, e. g. the difficulty of anaesthetizing rabbit cornea with 0.25% butacaine at pH 5.5, whereas at 7.4. the same concentration gives a considerable duration of anaesthesia. He suggested that this might ex--plain why local anaesthetics often fail to act in acutely infected areas, e. g. abscesses. Bieter (21) attributed the acidity effect to decreased hydrolysis of the anaesthetic. Rous and Drury (224) showed that adrenaline, despite the local ischaemia, gives definite acidosis: Hirschfelder and Bieter (111) claimed that this should therefore diminish anaesthesia.

Hirschfelder and Bieter also quoted the fact that the free bases of alkaloids are usually more active than their salts, probably because the salts are much more soluble in water, whilst the former are more soluble in fat, lipoids, and org--anic solvents. They thought that buffered solutions have a slightly more lasting effect than ones which are merely

alkalized. They concluded that the effect of a molecule of free base of local anaesthetic is more or less independent of its chemical nature, and that local anaesthetic potency should be a function of the degree to which it is hydrolysed, provided that the free base is sufficiently soluble to remain in solution or in a finely divided suspension. The effect--iveness of anaesthesia must also be a linear function of the pH of the tissue (an acidic local anaesthetic e.g. saligenin, is more effective in acid than alkaline media.) With local anaesthetics which are not simple salts, however, pH seems to play a small role, e.g. quinine and urea hydrochloride poten--cies are unaffected by pH, even in surface anaesthesia. This division of local anaesthetics into classes is one which should not be overlooked.

They advanced a principle which is important in the synthesis of new anaesthetics: in homologous series, the weaker the base, the more the free base is released by hydrolysis, and the greater should be the anaesthetic potency. This can be best achieved if the soluble anaesthetic salt is made from the ba--se and a weak acid instead of hydrochloric or sulphuric acids. These findings held for the conjunctiva and for intradermal injection, but not in infiltration anaesthesia or in the urethra. The authors considered that modifying factors may arise here: in deep tissues, or in the presence of urine, the anaesthetic salt reacts with sodium chloride which tends to decrease the hydrolysis and (by ionic interchange) to re--turn much of the anaesthetic to the form of hydrochloride, regardless of the acid used to form the salt (i.e. a buffer action occurs).

Höber et al (114) showed that pH can sometimes alter cytolytic changes in nerve membrane considerably, e. g. caprylate affects crab nerve at pH 5 or 6, but not at pH 8. (The species of the animal should not be overlooked).

Bieter (21) studied the uptake of alkaloidal base by nerve, and suggested that ionization of the alkaloidal salt produces an ion of the anaesthetic base carrying a positive electrical charge: the nerve structure, being negatively charged, takes up this ion.

Krahl et al. (146) used simple cells (Arbacia punctulata eggs and larvae) to try to determine the form in which local anaesthetics penetrate the cell, and the probable form in which, once inside, they enter into chemical reactions giving anaesthesia. Most local anaesthetics (with constant intracellular pH) needed a constant molecular concentration to give 50% reduction in cell division, irrespective of the total anaesthetic concentration, anaesthetic cation concentration, or external pH. The total local anaesthetic concentration required at pH 7.0 was 100 times greater than that needed at 9.1. They concluded that the anaesthetics penetrate only in the form of undissociated molecules, though in the larvae some compounds, especially cocaine, needed a lower extracellular concentration in solutions more alkaline than pH 8: they attributed this to the high pH values causing a partial breakdown of the semi-permeable qualities of the cell exterior, thus allowing some cation penetration. They considered that, un-

-like many other anaesthetic substances, it is the intrace--llular concentration of cation, and not the undissociated molecule, which causes the physiological effect.
They suggested that basic anaesthetics are local ones because cells at the site of application require so much anaesthetic to satisfy the laws of membrane penetration that relatively little is left to produce general anaesthesia. They noted an extraordinary tendency for the cations to escape from solu--tion in the intracellular aqueous phase to adsorb on, or combine with, cellular constituents.

Dawes (47) partially confirmed the work of Trevan and Boo--ck. He noted that, on rabbit auricle, many local anaesthe--tics are quinidine-like, and vice versa, although the two are not invariably linked. He recorded the order of infiltra--tion effects and quinidine activity as:- butyl alcohol, co--caine, butacaine, procaine. Variations (if guinea pig corn--ea was used) were ignored as being due to penetration diff--erences. His work on heart supported the contention (129) that local anaesthetic and quinidine-like properties charac--terize the free base. Not only are the most powerful local anaesthetics most active upon the auricle, but conversion into the quaternary salts (which stabilizes the cation) of some of the "cardiac" compounds could abolish their activity, just as a similar conversion of local anaesthetics abolishes their effects. The importance of the last cannot be ignored.
He decided that the free base can readily penetrate nerve and muscle, and once inside the cell it equilibrates with its cation again according to the equation:-

$$\underset{\text{(cation)}}{R_3NH^+} + OH^- \rightleftharpoons \underset{\text{(base)}}{R_3N} + H_2O$$

In this way cations of these substances could get inside the cells: previously it was though that the free base of local anaesthetics and quinidine substitutes is the active constit-uent because of its penetrant powers. It was further thought that curariform and atropine-like properties characterize the cation, but as this is unable to penetrate into cells (201) these activities must occur at the cell surface: this view has not won acceptance. However, Dawes' concept makes it feasible that the function of the free base is merely to facil-itate the entrance of the (active) cation. This conception is a most notable one.

Albert (4) concluded that, in Arenicola, narcosis depends on neutral molecules rather than ions, because weak bases, e.g. cocaine, are most effective in more alkaline solutions where they are least ionized, while weak acids, e.g. barbiturates, are least effective in these solutions because they are most ionized.

Löfgren (165) envisaged the local anaesthetic as contain-ing two constituents, the base B, and its corresponding charg-ed (ion) acid BH^+. (Like Ehrenberg (51) and others, he believed that the base decides the activity). In an aqueous solut-ion, the equilibrium $BH^+ \rightleftharpoons B + H^+$ depends on the pH of the solution and on the ionization constant of the compound. He maintained that much early work on minimum effective con-

-centration is useless, because of the use of unbuffered biological material, and lack of control of pH. Some authors did appreciate this and took steps to obviate it (23, 250 a,b, c,e,f), A striking experiment was the repetition by Mongar (194) of Elio's work (52) on guinea-pig wheals, using buffered instead of unbuffered solutions: cinchocaine was 34 times as powerful as procaine, as against the earlier estimate of only 10 times.

In surgery the natural body buffering probably conceals any variations in efficiency due to pH, but pH changes are obviou--sly most important in surface anaesthesia.

As the mucous membranes have a poor buffering capacity, the usual surface anaesthetics owe their efficiency to their high activity: but such drugs are often so toxic that they cannot be used much for injections. Consequently, Löfgren dismissed the idea that these substances have a special affinity for mucous membranes, e. g. procaine is said to be inactive on surfaces, but this is incorrect: since procaine solutions (c.f. lignocaine) are not stable for long at pHs more than 5, the surgical solution has a pH less than 5, and <u>this</u> solution does not anaesthetize mucous surfaces. If, however, the pH is increased to 7, or more, the surface effect is so increas--ed that the solution even surpasses an equal concentration of cocaine.

Gray and Geddes (91) stressed several important features. 1) the pH requirement varies with each drug and its concen--tration, since better precipitation of free base occurs with a strong solution than a weak one. 2) Excessive alkali may

precipitate the anaesthetic with consequent loss of potency (important in manufacture). 3) Inflamed tissue: the increas--ed vascularity of the area as well as pH may lessen the eff--ect.

The body represents one of the best systems of buffers that can possibly be obtained, and pH should therefore merit seri--ous consideration apropos of its effect upon the mechanism of local anaesthesia, and its influence upon the availability of the active form of the drug.

b. Differential effects.

That local anaesthetics elicit effects in various tissues has already been stated, but further consideration is desirable.

1. Nervous tissue.

In 1886 Alms (5) observed that cocaine produces sensory anaes--thesia without motor fibre paralysis: Bieter (21) noted that high concentrations can give motor paralysis, but it is diffi--cult to obtain. Gasser and Erlanger (78) suggested that thresholds vary amongst sensory fibres so that the time for blocking depends upon the functions mediated. They remarked that as the functions disappear in exactly the reverse order with compression blocks (see also (89)) it is plain that chemi--cal differences in affinity for the drug are not the full underlying cause. They claimed that small fibres are usually blocked before large ones, but blocking is not effected with any precision. Fibre size is a determining factor in nerve susceptibility to poisons, but it is not an absolute one: in small nerves the thinner myelin sheaths should permit easier

access to their axial protoplasm (the inference of axial act-
-ion should be noted, but the emphasis obviously lies in pene-
-tration into the nerve). They did not involve myelin in the hypothesis, but reasoned that cocaine acts by chemical combin-
-ation with the protoplasm, and as surface per unit volume increases directly with diameter increase, the smaller the fibre the greater will be the accessibility. (Burger (36) later endorsed this.) On this basis, washing should make the smaller fibres recover first: this is not so, as recovery proceeds in the reverse order to blocking. They justified their theory, however, by saying that in small fibres proto-
-plasmic chemical combination goes far beyond the point of block into stages of disorganization: on washing, re-organiz-
-ation is necessary before recovery can begin. Such a mechan-
-ism should cause fibre block on a systematic size basis: as this does not occur rigidly this can only be a partial explan-
-ation. Nevertheless, they claimed that the relation is good enough to support the claim of preferential sensory block, which was based on small sensory and large motor nerves. Th-
-ey suggested that Dixon's description of a cardiac vagal (motor) fibre being blocked more easily than a respiratory afferent one, was probably because the former was the smaller.

Hirschfelder and Bieter (111), too, discounted any differ-
-ence in anaesthetic efficiency in any type of nerve, whether sensory or motor. The work of Heinbecker et al. (108) on cat, where local anaesthetics first blocked action potentials in unmyelinated fibres, and then the smallest myelinated ones, progressing up to the largest myelinated ones was not regard-

-ed as upsetting their contention. Heinbecker and Bishop (107) with procaine, and Gasser (76) with cocaine, also proved that the C fibres are affected before the A ones. (Toman (272) classified the fibres as:- A = large myelinated somatic motor axons, and sensory fibres for touch, pressure, and proprio--ception. B = small myelinated preganglionic autonomic fibres, predominamtly with intermediate conduction speeds. C = un--myelinated postganglionic sympathetic and sensory fibres in--cluding those for pain. This classification is not rigid, as there is considerable sub-division and overlap.)
Obviously, some structural modification tends to delay block--ing in the second two types listed by Heinbecker et al., and myelin is immediately suspect. It will be considered in more detail later. Hirschfelder and Bieter listed activity loss as:- a) Vasoconstriction. b) Temperature. c) Pain. d) Touch. e) Joint and pressure sense. With intraspinal injection the curious fact emerged that motor activity went before joint and pressure sense. This may be because, intraspinally, motor nerves are more bare (accessible?) and hence more vulnerable (21). This concept is questionable: a more likely factor is that of accessibility to the (unmyelinated) motor nerve cells.

Lorente de Nó (167) reported that KCl and anoxia blocked groups of A and B fibres before the C ones. Toman (272) differed on the subject of asphyxia, but also noticed prefer--ential block of small fibres, quoting unpublished work on rabbit vagus with 1.0mM (1/40%) cocaine, where the A fibres were depressed first, and the C ones last. Lorente de Nó

claimed that phlorizin, like cocaine, is a true nerve narcotic, and yet it blocks A fibres first. Its mechanism is problem--atic, but he doubted if it interferes with oxidative energy release or any enzymes involved in maintaining the membrane or its resting potential.

It becomes clear from observations such as the above that there is more than one way of producing block, and even diff--erential block.

Löfgren (165) significantly remarked that local anaesthetic activity is readily compared on isolated motor nerves, but that conditions for practical local anaesthesia (i.e. sensory block in a complicated biological milieu) are difficult to survey in detail.

Sinclair and Hinshaw (248) compared procaine and compress--ion blocks: they concluded that the order of sensory loss in the latter is more consistent than it is with procaine. (This may well be a feature of dose and intensity thresholds, rather that a character of the drug.) Although the order differs with the two methods, they deduced that it is due to some form of selective action and not to chance, and they favoured the idea of physical and chemical differences in the fibres them--selves.

Frumin et al. (73) investigating dorsal root blockade, found that the root ganglion can be blocked by small procaine doses having little or no effect on the passage of nerve im--pulses in the roots: they were quick to note that the gang--lion cells are practically bare of myelin, having only a

thin connective tissue membrane on them, and they therefore assumed that the ganglion is more sensitive than either the dorsal root or the spinal cord. In clinical doses motor par--alysis regularly appears, suggesting involvement of the vent--ral root as well.

Toman saw no reason why all types of fibre should act by identical chemical mechanisms, as long as they have the same general explosive system, and this would obviously allow diff--erent types of block to exist. The flaw in this view is the apparent lack of specificity, for types of nerve, in blocking agents, and the general conformity of nerve to the current transmission theory.

Barlow (9) considered that nerve surface area, apart from influencing penetration, might govern drug susceptibility if it is a surface effect, and he suggested that there might be different enzyme systems in the sensory and motor fibres. He implied that the susceptibility of the particular enzyme determines the rate of nerve block production. He saw no reason why transport at mucous membranes and nerve surfaces should be identical, hence a local anaesthetic may be feeble on the eye but quite active elsewhere (i.e. it penetrates some tissues, but not others.) This may well be due to stri--ctly local factors, such as pH or cholinesterases.

2. Muscle tissues.

MacGregor (178) quoted observations on the use of procaine for local anaesthesia in myasthenia gravis: it sometimes accentuates the general muscular weakness, which led to the

idea that it either affects neuromuscular junctional transmission or the muscle directly. He used procaine and cocaine on skeletal muscles in vivo. Both the drugs reduced tension, cocaine being rather more powerful than procaine. Pre-curarization, to reduce muscular efficiency, potentiated the effects, suggesting that local anaesthesia and curare actions are similar. Gasser and Dale (77) and Brown et al. (31) had shown that sufficient curare to counteract nervous stimulation in normal gastrocnemius muscle had no effect on acetylcholine contractions in the denervated muscle: cocaine and procaine showed anticholinergic activity in this preparation, presumably indicating that cocaine and procaine act peripherally to curare. MacGregor suggested that local anaesthetics may directly reduce excitability or contractility of muscle fibres, but considered it improbable that they depress denervated, but not normal, muscle, as had been suggested (31). He suggested that the action is partially upon the motor nerve endings, and partially directly upon muscle fibres. MacGregor considered that similar (unpublished) experiments by Bülbring and Burn had not been conducted adequately, but still furnished evidence of a direct muscular action of cocaine, which, as elsewhere, stimulates in small doses, and depresses in larger ones.

As frog sciatic nerve keeps for 2-3 weeks at 0°C, Sollman and Estable (256) investigated the action of procaine on the excitability of frog muscle and nerve tissues, to see if it could imitate the hypothermia. They claimed that procaine depression of excitability is reversible only within rather narrow limits, and also that it depresses the excitability of

skeletal muscle nearly as much as that of motor nerve fibres (given effective penetration, which depends on prolonged exposure to the drug). They concluded that nerve depression by local anaesthetics is not a distinct phenomenon, but a manifestation of general "protoplasmic" depression, owing its practical usefulness to a favourable therapeutic index of anaesthetic potency as against local irritation and systemic toxicity.

They felt that the specialized uses of the drugs overshadow other effects, particularly as clinical anaesthesia aims to concentrate its effects upon sensory fibres, and to ensure reversibility. (If good contact is made by direct muscular or intra-arterial injection, anaesthetic concentrations of proc-aine can abolish the response of skeletal muscle to direct stimulation).

From experiments on animals and themselves, Sollman and Estable decided that sodium salicylate and sodium benzoate have local anaesthetic properties, but are poor procaine substitutes, especially as the former is more irritant. Procaine hydrochloride in relatively high concentrations over quite long periods induced irreversible paralysis in excised muscle and nerve: clinically this is not attained, due to dosage and removal of the drug by the circulation. Attempts to induce irreversibility in living animals failed, indicating the wide margin of practical safety with procaine. The danger of comparing in vivo and in vitro results too closely is again apparent.

Procaine depression of excitability grades so smoothly into death that they attributed it to the same general protoplas--mic toxicity, rather than to some fundamentally distinct "narcotic action".

Some decerebrate and tetanic rigidity can be relieved by procaine doses which do not affect voluntary movements or motor nerve stimulation responses,i.e. afferent proprioceptive fibres from muscle spindles are highly procaine susceptible (158).

However, Matthews and Rushworth (181) showed that procaine paralyses the large afferent and large efferent fibres of the soleus muscle simultaneously, but the γ efferent fibres (to the intrafusal fibre, 89) considerably earlier. They attrib--uted the selective paralysis of the stretch reflex to paraly--sis of the γ efferents rather than to paralysis of the affer--ent pathways.

Matthews (180) produced a selective effect with procaine (by paralysing γ fibres) getting some stretch reflex diminution before alteration of the motor tetanus. He admitted that the procaine effect differs according to decerebration by anaemia or section (89), but claimed that this is quantitative rather than qualitative.

In a single afferent fibre from muscle spindles Matthews and Rushworth (182) claimed that there is a two-stage response when cocaine is applied to nerve supplying the muscle:- 1) The fre--quency of spindle discharge falls suddenly to a new level similar to the one after ventral root section, apparently

due to γ fibre paralysis. 2). The spindle afferent itself is affected, and before its complete paralysis it will not transmit high frequency discharges. This appears to accord with the findings of Katz (138).

Procaine therefore produces a reversible γ de-efferentation of the intrafusal muscle fibres: such evidence opposes the concept of direct muscular excitability depression, and emphasizes that the situation is not so simple as was once thought.

3. Other Factors.

Sinclair and Hinshaw (248) raised the question of action sites, because in excised nerve the anaesthetic soaks inwards from all points of the circumference, whilst in man (109), and perhaps in all in vivo experiments, a concentration gradient may exist across the width of the nerve. The situation of the nerve and the site of drug application may well be the cause of this.

Henderson (110) disputed the assumption that tissues rapidly equilibrate with the blood stream, and that diffusion into the cell is also rapid. Storm van Leeuwen (259) used chloroform, ether, or a mixture, on cats, and found slightly more anaesthetic in the brain than in the blood: Henderson suggested that the various differentials between tissue affinities for anaesthetics might be largely attributable to blood flow differences. This is certainly a possibility, and one that is known to be important for general anaesthesia.

The time lapse before onset of anaesthesia has been shown by Laubender (154) to vary inversely with the logarithm of drug concentration. Gerlough (83) found that the duration of anaesthesia corresponds with the square root of the time of contact of the drug with the cornea. Hirschfelder and Bieter (111) related both these results to adsorption equations, and sharply dismissed some apparently contrary results by Sollman on the grounds of different routes of administration. In fact, it is likely that different times of onset and duration of anaesthesia are related to concentration, time of contact, and surface area of the exposed region.

Kato (136) considered that the minimal effective concentrat--ion (Cm) of local anaesthetic for a single fibre differs little from that of a nerve trunk. (If adsorption were the basic cause this would not be expected.) If a fibre is ex--posed to an anaesthetic slightly above its Cm value, block sets in almost immediately. From this Löfgren (165) opined that most of the time required for blocking is spent in diff--usion into the nerve, up to a critical concentration. Good local anaesthetics should possess high activity (low Cm value) and a high diffusion coefficient, and he emphasized that lat--ency and duration, together with activity and toxicity, are the criteria of usefulness.

Löfgren also vaguely alluded to some sort of temperature effect, although he stressed that its importance should not be over-estimated. It is possible that this goes no further than simple physical chemical laws, e. g. Van't Hoff's.

c. Anaesthetic structure and properties.

Some features have already appeared, and a general recapitul-
-ation of these is not proposed, but rather a consideration
of any especial features with seem to relate to mode of action.

Löfgren (165) stressed that the usual clinical local anaes-
-thetics have a typical composition: they are pronounced basic
esters or amides of aromatic carbonic acids. Their general
formulation runs:-

amino group - intermediate chain - aromatic residue

The amino group (generally secondary or tertiary) is of great
importance for specificity, and he claimed that virtually no
usable anaesthetics omit this group. He explained some excep-
-tions as a replacement of the hydrophilic amino group by
another hydrophilic group, e. g. 1) Hydroxyl, as in benzyl
alcohol. 2) Quaternary ammonium, although this may make the
drug primarily anticholinergic. Substitution of the aromatic
residue by an aliphatic one results in a considerably infer-
-ior effect.

He elaborated the importance of a balance between the hydroph-
-ilic and lipophilic parts of the molecule in surface reactions.
Indifferent (mainly lipophilic) substances, e. g. chloroform,
ether, follow the Overton-Meyer rule, even when applied as
local anaesthetics. Their distribution coefficients give a
measure of the important attractive forces (mainly van der
Waal's) between the narcotic and both lipoid and water. If
the molecules also have marked hydrophilic principles, e. g.

barbiturates, they should show more specific interactions with those of the conducting membrane layer: experiments by Schulman and Rideal (233) and Rideal (219) substantantiated this.

Löfgren envisaged the hydrophilic amino group in a local anaesthetic making contact with a suitable polar hydrophilic group in the membrane film (polar or "head" association), and that the lipophilic part of the anaesthetic probably helps to form the complex (this "tail" acts on the membrane film by van der Waal forces) so that penetration may occur.

From this Löfgren was not surprised that local anaesthetics do not follow the Overton-Meyer rule, since the distribution coefficients are important, but not dominantly so.

Although many narcotics have local anaesthetic properties, the typical aromatic amine type of local anaesthetics cannot be used as narcotics. Burger (36) stressed that they are purely local, e. g. if near peripheral nerve they affect it, but if on a central nervous organ they block transmission only in the area involved (i.e. in contact): moreover, dosage increase does not give general anaesthesia, but only systemic poisoning as a toxic level is reached. In doses of a quarter to one half of the lethal ones local anaesthetics usually produce (cerebral) convulsions: there is a rough parallel between anaesthetic activity and convulsive power (19). Narcosis can occasionally be produced, but only by such high concentrations that the test animals usually die afterwards (72). Benzyl alcohol produces an even narcosis, without convulsive activity,

and Löfgren believed that the hydrophilic amine group is involved, as it is a hydroxyl one: he surmised that its local anaesthetic action is the same as, or similar to, that exerted by general narcotics. (Beutner and Calesnick (19) have even questioned if benzyl alcohol should be classed as a local anaesthetic.).

Adams et al. (1) demonstrated a close correlation between oil/ water distribution coefficients and surface anaesthetic activities. MacIntosh and Work (179) further investigated this with aminoethanol derivatives, and found that the most potent compounds were mainly the most irritant, probably due to the high surface activity of their solutions.

In fact, it is likely that surface tension effect is somehow related to local anaesthetic activity, and also to irritancy: Luduena and Hoppe (172) with basic esters of benzoic acid, showed that greater irritancy and local anaesthetic activity coincides with increased length of the hydrophobic side chain. Luduena et al. (173) investigated irritancy, surface tension effect, and local anaesthetic activity of several local anaesthetics: they all lowered surface tension. Despite this, they concluded that local anaesthesia is independent of surface tension-lowering activity, thus a potent local anaesthetic (like procaine) may exist which has little water surface tension effect. However, they also observed that all the substances, when injected intradermally in sufficiently high concentrations into rabbits, produced inflammatory changes. They concluded that irritation induced by local anaesthetics is produced by a mechanism related to their surface activity.

Irritancy is a difficult thing to estimate, especially as that related to pH effects may be modified by the buffering action of the tissue fluids. The whole question is one that must await further substantiation.

Luduena et al. envisaged that local anaesthetic activity may result from a very high affinity for some specific structure in the nerve fibres. Some characteristics may increase the activity of the molecule without modifying the physico-chemical affinity, e. g. the presence of a long carbon chain increases the lipoid solubility of the molecule, provided that it does not interfere with the attachment of the polar group, or groups, in the drug to the receptors (i.e. the hydrophilic end).

To explain the increased surface tension effects at higher pH values they assumed that the un-ionized base is more effective than the cationic form. The form responsible for tissue irritation is unknown, but they considered that it might depend on both the organic cation and the un-ionized base.

MacGregor (178) attributed the direct depressant action of local anaesthetics on muscle and nerve to the free base, but Dawes (47) considered that procaine and atropine are similar because they are both tertiary alkamine esters, their properties being characteristic of both cation and free base. This again suggests that procaine is unusual in its class.

From butacaine Rider (220) decided that neither the free base, nor the ion, is the active constituent in a solution. He concluded that "in this case, at least", the activity of the salts is determined by the properties of the undissociated

molecule: he admitted that this contradicts accepted ideas about the mechanism of anaesthetic action, but dismissed these as being inaccurate or incomplete. Bein (10) later endorsed this concept.

Butler (37) declared that no specific chemical structure is necessary for general anaesthetic activity: in the aliphatic alcohol series anaesthetic activity was almost equally correlated with vapour pressure, oil/water distribution coefficient, surface activity, and water solubility. He quoted Führer's theory (74) that the paraffin hydrocarbons are anaesthetic but lack surface activity, and consequently the striking correla-tion found by Traube (274) between the two may not be essen-tial in the production of anaesthesia. He stressed the need for further researches on these correlations.

Höber (113) regarded narcotics as chemically 'indifferent' organic non-electrolytes which transitorily depress cellular functions and do not react chemically with cell components. They contact the cells by secondary valences or van der Waal's forces, changing the surface properties of various cellular structures and microstructures. These appear as changes of dispersity, hydration, colloidal aggregation, dissolving power, and adsorption affinity: Höber could not decide which of these reactions is the essential, or even the dominant one.

From the homologous series which Ludwena et al. (173) used they concluded that the stereochemical configuration which is responsible for lowering surface tension is the most important factor in the adsorption of the compound to protein or lipopro-

-tein in the tissue, but not necessarily for local anaesthesia.

d. Structural features of nerve.

Gasser and Erlanger (78) warned that the sheath may affect nerve penetration, but Lorente de Nó (167) maintained that diffusion rates into nerves are not limiting factors in mem--brane potential. He declared that cocaine would only require a few minutes to reach the surfaces of all the fibres in a nerve, and claimed to prove that penetration of connective tissue sheath and nerve by veratrine-like substances is exc--eedingly rapid. Nevertheless, he held that the sheath is not freely permeable to solutes, whether ionized or not. The connective tissue sheath decreases diffusion into the nerve largely because it keeps the nerve fibres tightly packed: if it is broken the interfibrillar spaces enlarge, and the solute therefore reaches the fibre surfaces more quickly.

This evidence might seem fairly conclusive, but Rashbass and Rushton (213) have shown clearly that the epineurium is an electrical barrier, and the work of Krnhevic (147) showed that it is a potent diffusion one as well, so the sheath must wield considerable influence upon drug action.

Another structural factor is myelin. Like the connective tissue sheaths its insulating properties have been known for some time, a considerable amount of information having been provided by Kato (136). Using myelinated fibres, he showed that the threshold strength of a nerve falls markedly near nodes. From observations of his own and of Tasaki (his collaborator) he concluded that an electric current excites the nerve only at nodes: an impulse is always set up at

the nodes, without regard to the position of the electrodes. Studies on single fibres revealed a striking phenomenon, viz. nerve conduction is instantly blockable by a drop of relatively dilute narcotizing or isotonic sugar solutions, or even distilled water, when applied to a nerve region where nodes of Ranvier are exposed. In a region containing three or more nodes, block occurred within $\frac{1}{4}$ second, and was usu--ally removed within 1 second of placing the fibre in Ringer. If the sheath alone was exposed to cocaine or urethane in Ringer, conduction was often retained for well over an hour, but if a node was similarly exposed conductivity disappeared within one second. Stämpfli (257) recorded similar results with potassium chloride.

Kato concluded that, like many stains, narcotics diffuse into the axis cylinder only through the nodes, and spread along the fibres on both sides of the point of entry. Finally, with narcotics at sub-critical concentrations, he observed an abrupt change in threshold (reducing excitability): recov--ery on removal was similarly abrupt.

Lorente de Nó (167) stated categorically that the myelin sheath is usually not an obstacle which would prevent substan--ces acting upon the nerve fibres, and postulated (168) that the nodes are unimportant in nerve function. Commenting on the idea that substances can only act at the nodes, he felt that such an assumption would be justified if test substances acted first upon unmyelinated fibres, but claimed that substan--ces such as potassium and calcium ions, and cyanide, act first upon myelinated fibres. He suggested that block can be obtained at thin places and bends in nerve fibres as well as at

the/

nodes of Ranvier: he considered it to be imperative to dis-
-cover histologically if the nodes are covered with a continu-
-ous myelin sheath. In fact this has probably been done ade-
-quately from a negative standpoint, i.e. if a sheath had been observed at the nodes it would certainly have received publicity by now.

In his comprehensive treatise Löfgren(165) recapitulated Kato's views fairly fully, and the fact that he had no criti-
-cisms to make cannot be ignored.

Lussier and Rushton (174) confirmed Kato's work, and pro-
-duced good evidence that the least excitable point is at the mid-internode (the threshold here being about 30% higher than elsewhere). Moreover, if the epineurium was intact these variations in excitability were virtually abolished. From this is it evident that myelin must not be mistaken for a perfect insulator, and they suggested that wisps of perineur-
-ium, remaining after epineurium detachment, may produce ano-
-malous results occasionally. This accords with the work upon sheath effects cited earlier (213,147).

The fact that many nerves are not uniformly susceptible, due to structural features, is something which may well in-
-fluence local anaesthesia, if the word "local" is interpre-
-ted in its strictest sense.

DISCUSSION.

Inevitably, the primary question relates to the validity of applying theories of general anaesthesia to local anaesthesia. The answer is relatively simple: there is little choice, as

all attempts have aimed at translating these theories into local anaesthetic terms, rather than formulating special theories per se.

This is not altogether unreasonable since the basic material in both cases (brain and peripheral nerve) is nervous, al-though in different body regions.

The looseness of the terms used is, however, unfortunate, e. g. "narcotics" may mean hypnotics, general and local anae-sthetics. Henderson (110) attempted to limit narcotics to the first two, but despite this, the ambiguity remains, and caution has to be exercised in much of the interpretation. Henderson also warned that anaesthetic changes in nerve may differ from those produced elsewhere, e. g. one concentration of drug may induce nerve anaesthesia, another decreases muscle contraction, and a third (often the largest) depresses muscle oxidation processes.

The thesis presented here is that local anaesthesia is not explicable in terms of any one theory, not from any particular inadequacy of these, but because it is considered that anaes-thesia can be produced in different ways.

Conduction failure may be due to increased threshold, fall in spike amplitude, or sub-critical membrane resting potenti-al. The last implies that the normal ionic balance is lost: this depends on metabolic processes as well as on diffusion gradients and membrane penetrability, hence any metabolic inhibitor might be expected, ultimately, to produce block. The potency of this seems to be indicated by the fact that a

widely quoted means of obtaining local anaesthesia (often accidentally) is anaemia, and this is presumably due to metabolic effects, although not necessarily direct ones on aerobic mechanisms.

An important topic nowadays is local anaesthetization by freezing techniques. Virtually no work has been done upon its mode of action, but it seems likely that it would be quite difficult to explain it in terms of the theories described previously. It is possibly related to Van't Hoff's law, producing a physicochemcial activity depression to sub-functional proportions. van Harrevald and Christensen have recently suggested (283) that a slow depolarization is produced, due to a reduced metabolism which cannot maintain the membrane potential.

Various conclusions about local anaesthesia have been drawn by other reviewers. Henderson (110) considered that adsorption might be a preliminary feature of narcosis, especially important in the central nervous system, but he felt that the Warburg theory was over-simplified. In his opinion, neither it, nor the Overton-Meyer one (which might explain the progressive storage of anaesthetic in body fat) adequately explain the peculiar inherent properties of narcotics. He was reluctant to admit permeability changes as a distinct theory, although conceding that a stabilization effect might occur. Butler (37), too, felt that no single theory could explain general anaesthesia, and he was particularly cautious about the adequacy of physical concepts in describing biological

functions (a view also held by Cohen and Cohen, 41). Toman (272) rightly remarked that the mechanism of nerve con--duction does not fit into any of the schemes of chemical med--iation devised for ganglia and neuro-effector systems. This emphasizes that results and theories must not be too readily transposed from one part of the nervous system to another.

The present discussion is divided into two sections. In the first, features which have limited either results or theories will be examined: in the second, an attempt will be made to resolve various topics which appear to be significant in this field.

a. Limiting factors.

1. pH. The practice of potentiating local anaesthetics with alkali indicated that the two are related, provided the drug is a basic one, thus the neutral compound benzyl alcohol is not influenced by pH (279), whilst the rare acid ones, e. g. sali--genin, react in the opposite way. The contention by Sollman (253, 254) that alkalization increases the effect on sensory fibres less than on motor ones is curious: it may be that the drugs are more effective on the former in the first place, and this could easily limit further improvement.

Attempts to link pH and surface tension effects with local anaesthesia (277) are largely invalidated by the contention (173) that the correlations between most local anaesthetics and surface activity are poor: thus pH changes probably in--fluence local anaesthetic activities rather than surface ten--sion ones. That pH can influence the cytolysis of nerve mem-

-brane seems probable (114), but even this relationship must not be allowed to obscure the primary (local anaesthetic) one, as may have occurred in some experiments (146). Furthermore, it has yet to be demonstrated that local anaesthetics exhibit cytolytic properties.

The buffering by the body is obviously important, and it is impossible to emulate such conditions in isolated tissues. Various authors have stressed the importance of minimizing variations in such tissues by keeping the pH constant (165, 251): Löfgren suggested that in some of the common local anaesthetic test methods an alteration of one pH unit may change the minimum effective anaesthetic concentration value tenfold. The link between pH and the stability of procaine, instanced by the same author, is also interesting: earlier, Bullock and Cannell (35) showed that at pH 4.3 about 2.5% of the drug is available, whereas at 7.5 about 75% is available. The lack of adequate pH control may have influenced the re-sults of many experiments found in the literature.

Finally, Höber's statement (113) that paralytic effect in-creases with rising pH in local anaesthetics, is independent of it in the alcohols, and decreases in general anaesthetics of the barbiturate type is most significant in respect of the close parallels sometimes sought between the three classes.

2. Species differences. That these exist is undisputed, ran-ging from the observation (124) that equivalent local anaes-thetic mixtures are more toxic to man than to guinea-pig, to the one (54) on the differences between succinylcholine and local anaesthetic action in man as against cats and dogs.

Work and Work (299) noted its existence, and Toman (272) reported differences in KCl effects on conduction in frog and earthworm fibres. In the latter and papers like those of Sh--anes (237,238) the gap is especially wide due to the division between the vertebrates and invertebrates. It is rather dis--turbing in this context to read Krnjevic's suggestion (147) that the action in similar frog preparations may vary in ani--mals obtained in the autumn from that found in frogs taken in the spring.

The warning by Keynes (139), on similar lines, about nerve transmission is understandable, especially as, for example, Lillie (160) based his views upon permeability on an inverte--brate. However, both sets of results do seem to be generally applicable which illustrates the difficulties attendant upon making this kind of prediction, or even of giving warnings.

3. Tissue differences. Much the same limitation occurs here, too, despite the claim by Lorente de Nó (167) that the elec--trical phenomena, at least, in muscle and nerve, are identi--cal. Shanes (243) believed that vertebrate muscle is more like invertebrate nerve (especially crab) than vertebrate nerve.

It has been shown (180,182) that the effect of procaine on muscle is to produce a preliminary fibre paralysis, and this may lead to some confusion, unless this effect is character--istic of procaine alone, which is unlikely.

Sollman and Estable (256) claimed that anaesthetic action in skeletal muscle and motor nerves is much the same, given effective penetration. The reservation at the end immediately creates a distinction, however, especially as they themselves admitted that muscle has to have a prolonged soaking in the

drug: moreover, penetration is probably less significant in sensory nerves, and, in particular, the important unmyelinated pain fibres.

4. Tissue distortion. It has been contended (167,168,169,171) that nerve connective tissue sheath produces no distortion of electrical potentials: this is disputed, especially in respect of the epineurium (58,147,174, 213). The opinion that nerve sheath is a potential barrier to drugs (78) was dismissed by Lorente de Nó (167) because of the rapid penetration by vera--trine-like substances, and he stipulated that the sheath is semi-permeable. The fact that veratrine labilizes the membr--ane (243) and increases its permeability creates doubts about the validity of Lorente de Nó's conclusion.

Kato (136) reported rapid penetration, provided that one or m--ore nodes were exposed, but found that myelin was a most pow--erful barrier. Thus, unless Lorente de Nó used unmyelinated fibres without stating so, there are two opinions about mye--lin, as well as about connective tissues. Kato's views have received more support (eg.174).

Recently the proofs of distortion of results by nerve conn--ective tissues have been listed by Shanes (243): the presence of such factors must surely affect drug action, in particular its onset and reversibility of action.

5. The experimental phase used. Brink and Posternak (28) tac--itly admitted the problem by envisaging that, in vivo, various substances may affect liminal narcosis by acting upon different cells or structures, thereby concealing orderly relations in relative effectiveness.

Differences between local anaesthetics in vivo and in vitro were tentatively suggested in 1930 (220). The evidence (256) quoted on p. 94 that procaine can cause irreversible paralysis in excised muscle and nerve, whereas, in vivo, the safety margin is unlimited, powerfully supports this.

Watts claimed (289) that various local anaesthetics on a brain homogenate substrate show a correlation between in vivo and in vitro results. However, the discrepancies in creatine phosphate levels with central narcotics, quoted by Barlow (9), were only remedied by the introduction of McIlwain's techni--que of electrical stimulation of the isolated material. It is difficult to see why local anaesthetics apparently worked better on brain than central narcotics: practical usage does not reflect these results.

Welch and Bueding (291) have claimed that the only enzyme action seen in vitro, which has been confirmed in vivo, is that of eserine. This is an assertive remark, but the gulf between the intact animal and isolated tissues has frequently been confirmed (262, 15).
However, to preclude results on these grounds would eliminate most of the information there is, hence they must be utilized, but with reserve.

6. Homologous series. Sexton (235) noted, when relating bio--logical activity to physical properties that, in homologous series, there is a peak of activity as the series is ascended, and a decline thereafter. Nevertheless, the convenience of using related compounds is undoubted (this is particularly

true for manufacture, too) especially to minimize errors from factors such as differences in diffusion and detoxication rates, and various authors have employed them (11,56,135). This is perfectly acceptable, and it is not surprising that such series have shown some regular features which allow cer--tain predictions to be made (e.g. concerning the Overton-Meyer theory, 36), or which show certain correlations (e.g. between surface activity and local anaesthetic potency), but their use must stop there. It is wrong to carry conclusions from them to unrelated substances. Luduena et al. (173) ad--mitted that the surface tension relationship cited above exis--ts in homologous series, but they emphasized its absence when comparing compounds with radically different structures: this must be true of the whole variety of substances embraced by the term "local anaesthetic".

7. Use of models. Models have been used frequently, the most famous one being Lillie's iron wire. The Overton-Meyer theory was derived from a simple one, which has been much criticized.

The difficulty of constructing a model of nerve, with its three concentric layers of core, sheath, and external medium has been emphasized (167), especially because the intermediate layer must be the site of an electromotive force maintaining a potential difference between the conductors each side of it, i.e. a resting membrane potential: in other words, it has to be dynamic.

Nevertheless, models have been, and must be, an important, and sometimes the only, bridge between a theory and the com-plete tissue or system.

8. Temperature. Löfgren (165) felt that its effect should be considered, although rating it as being of less consequence than pH.

It is certainly important in freezing anaesthesia, especi--ally if the claim (167) that hypothermia acts identically on action potential with oxygen lack or depolarizing agents is correct. No conclusion can be drawn from this electrical re--action alone, but the possibility remains that anaemia and refrigeration may produce local anaesthesia in a similar fas--hion: however, it has also been suggested (243) that low temperatures limit changes in membrane channels, and also reduce the thermal vibrational energy of molecular components, both of which would tend to promote membrane rigidity (and h--ence stability). This seems to be a more likely approach.

9. Anaesthetic ratings. Potency ratios are often used in these studies. They utilize several test methods, and it has been indicated (165) that these vary considerably, because some workers study the minimum effective concentration, others the effective duration, and yet others the latent period. Löfgren applied new uniform tests to the compounds he used, and Hamilton et al.(99) introduced a system of ratings based on appropriate drugs for each method of administration. Lit--tle evidence exists of acknowledgement of the comments, and yet it is undeniable that lack of uniformity must surely in--fluence quantitative results. Many anomalies, no doubt, arose from pH factors.

Qualitative ratings, too, are important, as few drugs have

a single effect. Atropine, procaine, quinidine, pethidine, papaverine, have been listed (4) as having the following com--mon properties, local anaesthetic, spasmolytic, analgesic, cardiac retardation, and anticholinergic effects, in a number of tissues. Each drug has one property highly developed at the expense of the others, but, even so, such multiplicity may cause some confusion.

These comments obviously apply to other drugs as well, and the view that benzyl alcohol is a general, rather than a local, anaesthetic illustrates this point clearly.

10. Procaine. Despite its wide use experimentally, there are grounds for doubting if procaine can be regarded as a standard local anaesthetic. For example, it can be injected intraven--ously, a property only shared by lignocaine. (From the lit--erature available, however, (incl.51,87,165) it seems that lignocaine acts in a 'normal' local anaesthetic fashion).

Other experiments have been described (32, 206, 249) sugg--esting that procaine behaves differently from other local anaesthetics. Toman (272), commented on the apparent anomal--ies of it, especially underlining that its activity on muscle tissues seems to be more highly developed than is usual in local anaesthetic drugs.

Skou (251) showed that it depresses all peripheral excitable tissues, while Sollman and Estable (256) suggested that it is more effective on skeletal muscle than nerve: Toman remarked that death from over-dosage is usually due to cardiac arrest.

From the above it is clear that there are many limitations

set upon the results of local anaesthetic researches. It is problematic as to how much weight attaches to each aspect, but it is clear that, if taken to their logical conclusions, virtually every result would be invalidated on one score or another: that local anaesthetic theory does show some relation to practical activity of the drugs indicates that this must not happen. Rather, the results must be taken and used cautiously in lieu of further proof, which it is to be hoped, will be forthcoming.

b. Features for resolution.

It remains to be seen if any points can be resolved which bear on local anaesthesia.

Such discussion must necessarily be confined within the limits for which information is available, and will attempt to answer certain definite questions.

1. Is local anaesthesia a surface activity ?.

Lillie's model showed characteristic surface changes during activity, and the view was expressed (165) that the highly organized layer of molecules and metal ions of the membrane is involved in the transport of impulses. More recently this opinion has been supported (4,117,243), and the membrane consequently indicated as a likely site for hypnotics to act. The attempt (78) to relate differential blocking effects to fibre size is an expression of a belief that surface area, at least, is important.

The linking of local anaesthesia with both surface tension effects and adsorption constitute an admission that some effect occurs at the nerve surface. The important work of

Bennett and Chinburg (12) cited the cell membrane as the prob-
-able site of action of local anaesthetics.

It was suggested (165) that the velocity of the process after contact with the node indicates a surface reaction in the plasma membrane or in the region immediately adjacent to it. Other workers have commented on the speed of action of local anaesthetics (24) and also of calcium ions (175).

The permeability theory merits very close attention with many local anaesthetics, and its relation to activity at the surface, by which it can influence ionic exchanges, is obvious. Stabilizers probably act in this way (243), but the slower acting labilizers could behave differently.

On balance, therefore, it is probable that many local anaes-
-thetic drugs act at, or around, the surface of the cell.

2. What is known about the membrane ?.

Cremer stipulated that the core of a nerve is surrounded by an insulating layer or lipoid. This suggested that myelin fulfils the latter rôle: it fails to explain the unmedullated fibres, but it was implied (9) that neurilemma contains enough fat to fulfil Cremer's general terms.

It has also been suggested that the membrane need not be anatomically distinct, and that myelin, too, is quite a fluid entity (167). This may be satisfactory if metabolic concepts are held, but it rather opposes the tenability of permeability ones.

As early as 1932 the membrane was envisaged as a continuous layer of fat, or as an emulsion containing fat and protein, the latter beingcapable of altering permeability (111),

while Löfgren (165) believed in the existence of a strongly organized lipoprotein film combined with metal ions. Moreover, von Muralt (285) claimed to have photomicrographed the membrane in ultra violet and polarized light.

It has recently been emphasized (243) that myelin sheaths, Schwann cells, and connective tissue sheaths are relatively rigid, and must not be mistaken structurally for the membrane which is only found at the nodes. Myelin is regarded as a double cellular membrane, derived from the surrounding Schwann cell (82, 222), which has similar dimensions (61,62, 63), and comparable electrical characteristics (116), reactions to local anaesthetics (266,267), depolarization effects by KCl (128,266), as the physiological membrane.

Using local anaesthetics, it was concluded (250 f) that stabilization is associated with a tendency of the lipoid phase of the membrane to expand, and, most significantly, a similarity was found between myelin and nodal membranes. Moreover, X-ray and polarized light studies (62,63,64,65,230) have suggested that the lamellar structure of myelin is essentially the same as the physiological membrane, i.e. a double layer of lipoid molecules, perhaps bound at each aqueous interface by a layer of protein (46). The active membrane is relatively thick (probably up to about 100 A°).

The presence of fat in the membrane is generally acknowledged, and a recognizable structure is likely, although the question of porosity is particularly bound up with the validity of the permeability theory.

Barlow's comment that neurilemma contains fat (9) immedia-
-tely provides a reminder that myelinated C.N.S. fibres have
no neurilemma, in contrast with similar peripheral fibres
(This is an important factor in regeneration of the latter).
It is probable that most work on peripheral nerve employed
medullated fibres, and it is therefore an unavoidable infere-
-nce that the possession of a neurilemma must be regarded as a
factor, distinguishing central nervous tissue from peripheral
nerve, which could influence drug actions, no matter whether
they are general or local anaesthetics.

3. What is the role of myelin ?.

Various authors have demonstrated that nerves are only excit-
-able through the nodes (127,136, 174, 213). Increased extra-
-cellular potassium (176), or Ringer made hypertonic with NaCl
(177), raise the conductance of a single node of Ranvier: how-
-ever, salinity changes affect the myelin also (266, 267), so
the overall effect of varied tonicity is questionable, as in-
-deed whether the node is, in fact, more affected by it or not.

The threshold of stimulation is up to 30% higher in the mid-
internode region, and on this basis it is clear that myelin
exercises a form of protective function, apart from any accel-
-eratory one with which it evidently invests nerves. It is
therefore to be expected that unmyelinated nerves should be
more susceptible to drug action than myelinated ones: even
Lorente de Nó (167) was unable to claim that there are no ob-
-stacles at all to unrestricted diffusion into, and out of,
the nerve.

4. What causes differential effects ?.

Evidence for differential block has been advanced (12, 138), the latter authors stipulating a blocking of high frequency impulses, due to slow membrane equilibration. This is obviou--sly important in view of the present concept (2,49,89,295) that receptors can signal stimulus intensity, by means of im--pulse frequencies. The block of high frequency impulses would surely lead to differential effects. Moreover, Granit (89) has claimed that the sensations of touch and pressure are merely distinguished by the numbers of stimuli involved, thus the scope for 'selective' effects appears to be quite wide. Much the same may hold if he is correct in his supposition that the leading principle in sensory discrimination is one of a differentiation by pattern (e.g. warmth receptors pro--duce impulses in an irregular "spluttering" fashion, but at considerably lower frequencies than cold ones).

The work by Katz (138) is of interest because the action of procaine upon the receptors shows the normal block withou--t depolarization effect. It raises the possibility that the sensory arc may be more sensitive to local anaesthetic in the vicinity of the receptor than in its nerve. The pre--ferential blocking of the γ efferents reported by Matthews and his collaborators (181,180,182) lends support to this vie--w, although also referring to muscle receptors. Certainly it should be borne in mind that many local anaesthetic in--jections are made into regions, particularly subcutaneous ones, which are rich in receptors. Even with a medullated afferent nerve there is bound to be a gap between the myelin

sheath and the receptor itself: it is suggested that at this gap, and perhaps the receptor itself, are points of hyper-sus--ceptibility to anaesthetics. The "off" response with pro--caine seems inexplicable at present: it may be due to de--polarization of the resting nerve which is in a highly excit--able condition, ready for immediate stimulation (Katz's dyn--amic state), or it may be another anomaly of procaine.

The sensitization effect cited for several general anaesth--etics might be explicable as some sort of labilizing action.

The observation (167) that KCl and anoxia block myelinated fibres first is curious, but raises two suggestions:- a) the metabolism of these faster conducting fibres is higher than the others, and is more susceptible to oxygen lack, b) as Toman (272) suggested, fibres may act by different mechanis--ms which, however, possess the same explosive type of action. However unacceptable the latter may seem it must be admitted that central and autonomic neurohumours vary, just as nerve conduction and end-plate transmission probably differ. The fact that synapses are more susceptible to drug action than nerve cells, and neuromuscular junctions less than either (36), lends some support to this. In all these results it should be remembered that it is easier to obtain "normal" reactions from motor than sensory nerves, and this must inevitably colour all the conclusions.

Sollman and Estable (256) claimed that the siting of local anaesthetics is important, i. e. they are usually pl--aced close to the structure to be anaesthetized. At the

best this is half a theory, as it may explain preferential action on peripheral nerve, but not the differential effects on the various fibres in a compound nerve.

Finally, the results of Forbes et al.(70) are most note-worthy: they reported that, in general anaesthesia, electri-cal representation of sensory stimuli reaches the cortex with undiminished, or even augmented, intensity, but due to the depression they are not recognized. Clearly the drugs involv-ed were not behaving in a local anaesthetic fashion, and if this is substantiated it must raise some doubts about the act-ivity which is thought to be common to both general and local anaesthetics, although action sites are obviously implicated.

5. What is the influence of the structure of the drug ?.

The importance of structure was appreciated early (191). In fact, three action phases may be distinguished:- a) The union of the drug and the receptive surface, b) Its fate there, c) Its destiny thereafter.

a):- It is evident that molecular structure does control the uptake of a drug, and Löfgren (165) has formulated a standard local anaesthetic framework, whose basis is the possession of both hydrophilic and lipophiloc groupings. Excessive hydro-phile properties may produce interaction with the membrane and different anaesthetic activities, perhaps even lowering them (36).

The 'typical' hydrophilic grouping is a tertiary amine one (36, 165, 272), which apparently reacts well with suitable ones in the membrane: this character is absent is many de-pressants which, in large concentrations, have local anaes-

-thetic effects.

It is most significant that this group in benzyl alcohol is a hydroxyl one, and this drug produces an even narcosis without convulsions. Increased lipoid solubility with lengthening carbon chains has been remarked (173), but it is clearly sec--ondary to hydrophilic properties (165).

b):- Some sort of blanketing effect has been suggested as many drugs act in the form of undissociated molecules (10), and reference to them (111,220) and neutral molecules (4) appears in relation to local anaesthesia.

The largest body of opinion favours the concept of hydrolysis of the drug. Certainly, the best local anaesthetics are made from weak acids and are thus easily hydrolysed (111, 146), al--though Rider (220) practically rejected this view because but--acaine was not as strong on hydrolysis as anticipated. The fallacy of only using one drug on which to base a conclusion is exposed here.

c):- Assuming that changes of a hydrolytic nature occur, the free base merits attention. Increased anaesthetic activity with alkalization supports this (95), and the relationship has been recognized to some degree, at least, in muscle and nerve (178,279,111,173). In the last, Luduena et al. attempted to relate local anaesthesia to surface activity, but even here, the free base was the most effective form. On balance it seems quite clear that the importance of the free base lies in its penetrant powers into the nerve.

A different view, based on procaine, is that, as it is more

effective at pH 7 than 9, the cation must be involved (261). This is at variance with the results of various authors inclu-ding Löfgren, and it appears that the conclusion is based on an anomalous observation. Nevertheless, it serves as an intr-oduction to the concept that the efficacy of local anaesthet-ics depends on cations acting intracellularly (146). This idea has received support, and the stabilization of the cation, with subsequent loss of local anaesthetic powers, strongly su-pports this view (47).

6. Is penetration important ?.

It was early suggested that rates of action and diffusibility might be as important to local anaesthetics as to other drugs (292).

If local anaesthetics act by film penetration, they might dis-play some haemolytic activity. Gessner et al. (84) investig-aged about fifteen of them, and all produced haemolysis: high concentrations of weak anaesthetics (e.g. procaine) were re-quired, whilst the reverse was true of potent ones (e.g. cinc-hocaine). Skou has suggested (250b) that the toxic effects of local anaesthetics on peripheral nerves is due to the same changes that produce haemolysis.

Since then the importance of penetration has been cited fre-quently, and, significantly, in connection with many effects, including surface tension (274), adsorption (112), anticholi-nesterase (93), potassium synergism (111), and permeability (243), the last author stating that high lipoid solubility of many compounds used in narcosis is consistent with this view.

The form in which penetration occurs has been variously sugg--ested as undissociated molecules (146), neutral molecules (4), and free base (250 a,c.). The importance of the last is well supported (47,88,100), and Skou (250a) claimed that the anaesthetic content of nerve lipoid is directly proportional to the free base, but that the cation might have a part to play: he also showed quantitatively (250 f) that the rela--tive uptake of procaine by nerve lipoid is increased by raising the pH.

The link between free base and penetration seems inescap--able, and the view, expressed in 1955 (88), that, once through the membrane, the free base dissociates and acts on axoplasm to give blocking, links this section with the preced--ing one.

CONCLUSIONS.

Various theories have been advanced as being valid for local anaesthesia. Most authors appear to have recognized the shortcomings of such a policy: the danger lies, not in apply--ing a theory to local anaesthesia, but in taking results from general anaesthesia of the central nervous system and applying them indiscriminately to peripheral nerve. It has rightly been said...."most axonology seems considerably re--moved from problems of central nervous function, except by broad analogy". (272)

This statement is not upset by the observation that, just as general anaesthesia is inexplicable by one theory alone (and the use of unusual agents such as progesterone (185) and xenon

(27) amply confirms this), the same is applicable to local anaesthesia. Many substances can stabilize the membrane or inhibit metabolism, but are not local anaesthetics. On the other hand, many local anaesthetics seem to act in ways ex--plicable in terms drawn wholly, or partially, from several theories: that the same theories are not named each time strengthens the belief that various mechanisms are involved, and block by such diverse agencies as refrigeration and oxy--gen under high pressure (207) confirms this.

The fact that a model, or isolated tissue, is no substit--ute for the living cell or tissue in its natural surround--ings is inescapable: that models, at times, provide informa--tion which would be entirely lacking otherwise is true, but, as with general anaesthetics, they must not be used as a ba--sis for generalizations on local anaesthesia.

In conclusion, it is possible to compile a list of salient features which are obviously important, and most of which have been fairly clearly proved.

1. The theoretical investigation of local anaesthesia and its practical application are often unrelated. A strik--ing example is the pH effect upon the action of pro--caine at mucous surfaces.

2. The present widely-accepted views on nerve impulse tran--smission give added prestige to views on nerve block being caused by permeability changes. That many local anaesthetics stabilize membrane conditions is very note--worthy.

3. That some agents block by depolarization is undeniable, but since the nerve impulse is accompanied by a wave of depolarization, it is clear that, if drugs blocked in this way, their blocking effect would be preceded by

stimulatory effect, and this is not borne out in clini-
-cal practice.

4. From studies of conduction it is to be expected that inhibition of metabolism may ultimately cause block, but it is a fairly slow process, due to such factors as the anoxic reserve.

5. Permeability or metabolic effects occur at, or in, the surface, and this must be partially governed by lipoid solubility (Overton-Meyer theory) and also by adsorp-
-tion (Warburg theory).

6. Sooner or later the drug penetrates the cell, and the free base is the agent for achieving this in most local anaesthetics (of the basic type).

7. Because of this action of the free base, the pH of the anaesthetic solution, and the modifying one of the surr-
-ounding medium, have an important part to play in the efficacy of the drug.

8. There is a growing body of evidence that the free base secures penetration into the cell, and that it is then converted into the cation, which is, in fact, the true 'nucleus' of local anaesthetic activity.

9. Considerable variation in activity arises from connec-
-tive tissue, etc. around the nerve fibres, because of the impedance it causes to movement of the drug. This, coupled with site of injection, and pH, may explain many of the delays in onset of drug action.

10. Myelination provides a further barrier to drug action, and may explain why drugs take longer to act on medull-
-ated nerves, since the drug has to effect an entry at the nodes of Ranvier first. It effectively ensures that under normal conditions (of oxygenation, etc.) the un-
-myelinated fibres (and this includes the ones carrying sensations of pain) block first.

11. Further differentiation is provided by partial blocking, which disrupts some impulse frequencies in nerves, whilst leaving others unchanged. By virtue of this, certain intensities of sensation may be selectively eliminated before others.

12. There is some evidence for preferential local anaesth-
-etic effects in the vicinity of the sensory nerve end-
-ings, i.e. at the receptor, or immediately adjacent to it. This might well allow a further differentiation of effect, especially if some endings are more susce-
-ptible than others.

13. The peculiar susceptibility of the nodes of Ranvier to

drug action lends support to the saltatory theory of nerve conduction, although it is not vital to the present study.

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